Asbest Chrysotile Cohort Study
Data Analysis Plan

Program Title	Large-scale retrospective research of risk of oncological disease caused by occupational exposure to chrysotile asbestos containing dust		
Specific Protocol Title	**A retrospective cohort study of cancer mortality in employees of a Russian chrysotile asbestos mine and mills**		
Ethics Approval Ref No.	IEC No. 12-22, September 2012 (annual renewal)		
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Background

The rationale and design features of the Asbest Chrysotile Cohort Study (ACCS) have been published previously (click here). A detailed description of the Cohort Profile is under review for publication. A very brief summary is given below.

There are different forms of asbestos, broadly divided into the amphiboles (actinolite, amosite, anthophyllite, crocidolite, and tremolite) and serpentine (chrysotile) groups. All forms of asbestos are classified as human carcinogens by the IARC Monograph Programme on the Identification of Carcinogenic Hazards to Humans (click here).

The current study seeks to obtain:

- Quantification of the risks of lung cancer and mesothelioma specific to Russian chrysotile asbestos exposure, e.g. for relation of risk to duration and intensity of exposure;
- Improved estimates of risks of cancer in women, as the ACCS, unlike other cohorts, contains a high proportion of exposed women;
- Estimation of the risk of cancers of the ovary and larynx (classified as asbestos-related cancers in 2012) and other cancers, especially those for which there is limited evidence of an association with chrysotile (cancers of the pharynx, stomach, colon and rectum).

Studying these questions may have implications for cancer prevention and early detection, cancer services planning, compensation, and estimation of the cancer burden due to the effects of chrysotile exposure in the Russian Federation and worldwide.

Number study participants	35,837 (37% females)	Follow-up period	1/01/1975-31/12/2015
Study research questions	• To estimate the relationship between mortality due to lung cancer and mesothelioma, and occupational exposure to chrysotile; • To examine, for chrysotile, this association for other cancer sites already recognised or suspected as associated with asbestos exposure; • To characterize the effects of duration and of intensity of exposure and latency period on cancer mortality.		

	• To examine cancer risk specifically in female workers.
Specific hypothesis under study	Occupational exposure to chrysotile is associated with increased cancer mortality, particularly for cancer of the lung but also for other specific sites.

Data Sources	
Study type	Retrospective cohort study
Data sources	**Cohort enumeration:** • Personal employment records from the JSC Uralasbest eligible enterprises. **Vital status:** • Civil Acts Registration Office (ZAGS) of Sverdlovsk oblast reporting on births, marriages, divorces, name changes, and deaths for the time period from 1975 to 2015; • The Pension Fund of the Russian Federation reporting on people receiving pension from 1998 to January 2015; • Federal Migration Bureau (FMB) reporting on address changes and migration outside Sverdlovsk oblast in the last decade; • JSC Uralasbest database of current workers; • Additional data sources were used for validation of vital status including Uralasbest Veteran's council, surveys among Uralasbest workers in 1995 and 2017, and electoral lists for the town of Asbest. **Cause of death ascertainment:** • Civil Acts Registration Office (ZAGS) of Sverdlovsk oblast providing original death certificate information (causes of death in its original text); data validated using information from Medical Information Analytical Centre (MIAC) of Sverdlovsk oblast for the period January 1990-May 2015. **Exposure data:** • Regular dust concentration measurements performed by and recorded by the Central Laboratory at JSC Uralasbest, from 1951 (factories) and 1964 (mine); for more details (click here). • Parallel measurements of dust and fibre concentrations conducted in 1995, 2007, and 2013 – 2014; for more details (click here).
Study population eligibility criteria	Employees at JSC Uralasbest with at least 1 year of employment between 01/01/1975 and 31/12/2010 in mine, any factories, auto-transport or external rail transportation, central laboratory, and explosives units.
Person-year calculation	Starts on the 366th day of continuous or intermittent employment in an eligible enterprise after 01/01/1975. Ends at first of 31/12/2015 (end of follow up period), date of death, date of emigration outside the Sverdlovsk oblast, or last known date alive.
Analysis package	SAS, R and Stata

Analytical Strategy	
Outcomes	Site-specific mortality from cancer of trachea and lung (C33-C34), mesothelioma (C45, including and excluding "Malignant neoplasm of pleura" C38.4), larynx (C32), pharynx (C10-C11, C13-C14), stomach (C16), colon and rectum including anorectal (C18-C21), ovary (C56), and "all other cancers" (ICD-10: C00-C97 excluding those mentioned above). All-cause mortality and non-malignant respiratory mortality will also be analysed.

Exposures of interest	Main exposure of interest: • Individual cumulative dust mg/m^3-years, accumulated over each individual's complete employment history at JSC Uralasbest. Individual dust exposures are cumulated over the duration of employment at JSC Uralasbest, by linking each distinct work period through job title and work unit with the dust concentration measurements carried out at the respective work places. Details are described in a separate publication for the exposure assessment and assignment (in preparation). Alternative exposure of interest: • Individual estimated cumulative fibre/ml-years, using conversion factors estimated from parallel dust and fibre measurements performed in 1995, 2013 and 2015/2016.
Main covariates:	• Age • Sex • Birth cohort (birth decade by default, wider categories for rare cancers)
Exploratory covariates:	• Employment characteristics such as 'main area of work' (mine and transport, factory and laboratory, or both), 'year of first employment', 'age at start of employment', or 'duration of employment'.
Lag periods:	Lags: To account for the delay between exposure and cancer diagnosis, a lag period will be applied in all analyses. The main analyses will use a lag of 5 years. Longer lags of 10 and 20 years will be applied to lung cancer and other cancers in sensitivity analyses where the number of cases is sufficient.
Tabulation of cohort characteristics	1. Constitution of the cohort (vital status by predominant workplace and sex) at the end of 2015 (end of follow up period); 2. Person-years of observation in the Asbest Chrysotile Cohort by sex, age group, and calendar year; 3. Tables separated by vital status (alive, deceased, censored by sub-groups), sex, duration of employment (1-5, 6-20, > 20 years), and decade of first employment; 4. Number of deaths and death rates (per 100,000) from all relevant causes in the Asbest Chrysotile Cohort by sex, age group, calendar time of death, main workplace (mine, factories, both), and birth cohort; 5. Number of workers and average age at start of employment in relation to duration of employment at JSC Uralasbest and cumulative dust exposure by sex; 6. SMRs relative to Asbest town and Sverdlovsk Oblast, for time periods where comparable disease information is available. 7. Mesothelioma, as a cancer highly specific to asbestos exposure, will be described in detail as number of observed cases is expected to be small due to the rarity of the cancer and the age composition of the cohort.

Exposure-response relationship (categorical models)	The exposure-response relationship for lung cancer will be investigated using Poisson regression comparing no professional dust exposure (reference category), to tertiles of exposed workers and to the 10% with highest exposure. The tertiles will be assessed with cumulative exposure based on all exposed workers, male and female. The exposure-response relationship for other cancers will be investigated using Poisson regression. The exposure categories will be: no professional dust exposure (reference category), exposed below and above the median of exposed workers. All analyses will apply a 5-year lag as described above and be stratified by sex, birth cohort and attained age. All models will be stratified by sex and adjusted for birth decade to account for potential confounding of tobacco smoking (results from tobacco survey under review). To account for the fact that women smoke differently in dust-exposed and other areas of JSC Uralasbest the first tertile of exposed women will be used as reference category for the women.
Continuous exposure response analyses (linear excess risk models)	Model A: Linear survival model showing risk by cumulative dust mg/m3 –year: the most powerful model able to allow for strong age-dependency, assuming the response is linear. Model B: Lung cancer death rates by duration of employment during which dust exposure was estimated as greater than zero (B-1) and average intensity of dust exposure (B-2). These models will be re-estimated using the modelled exposure to fibre (as discussed above as an alternative exposure of interest).
Further explorations	The results from the analyses described above will guide more in-depth and additional analyses if needed to better understand them. An initial list of further explorations is outlined below. • Dust exposure weighted for "percentage of working time in exposed areas" as recorded by the Central Laboratory Unit of JSC Uralasbest; • Exploratory covariates including 'main area of work' (mine and transport, factory and laboratory, or both), 'year of first employment', 'age at start of employment', 'duration of employment'; • Various restrictions of the study population e.g. to workers starting working after 1975, workers predominantly working in factories/central laboratory, workers predominantly working in the mine/explosives unit/external rail/auto-transportation; • Mortality rates beginning 5 or 10- years after the end of employment (to test for healthy worker effect); • Testing for cumulative dust exposure-response linearity (Cox regression models with splines); • Exposure-response relationship analyses using log-transformed cumulative dust exposure indices; • Nested case-control study on lung cancer matching cases to controls on period of first employment, age at first employment, and duration of employment to analyse

	average intensity of dust exposure. • Standardized mortality ratio (SMR) assessment for all-cancer mortality, mortality due to lung cancer if the tabulated (by sex, age groups, and calendar periods) cancer mortality statistics data are partly available for study period either for Asbest town, or Sverdlovsk oblast, or both. • Application of other lag times as described above

Work plan

The following shows the order in which analyses are performed.

Priority 1 Description of cohort and exposure-response relationship using categorical models:

- Tabulation of cohort characteristics;
- Calculation of Poisson regression-based relative risks for the endpoints defined under "Outcomes", relative to no professional dust exposure, tertiles of exposed workers and 10% of highest exposed;
- Description of mesothelioma deaths and relative risks estimations as numbers allow.

Priority 2 Continuous exposure response analyses:

- Description of the relationship between mortality due to lung cancer, and due to mesothelioma, using linear excess risk models (Model A);
- Calculation of lung cancer death rates by duration of employment with non-zero professional dust exposure and average intensity of dust exposure (Model B);
- Estimate the association between other cancer sites and cumulative dust exposure and duration of dust-exposed employment, using linear excess risk models (Models A and B);
- Above mentioned analyses will be re-calculated using the modelled exposure to fibres.

Priority 3 Further explorations:

- Use of alternative measures of exposure as described under "further explorations" above;
- Use of various restrictions of the study population;
- Test for non-linearity of exposure-response (Cox regression models with splines);
- Characterization of effects of duration and intensity of exposure as well as different latency periods on cancer mortality, using linear excess risk models and nested case-control study design. .

References

Publications prior to the main analyses (already completed and available through Open Access):

1. Study design (Schüz et al., Cancer Epidemiol. 2013)
2. Time trends in dust levels (Schonfeld et al., Ann Work Expo Health. 2017)
3. Conversion factors between dust and fibres (Feletto et al., Int J Hyg Environ Health. 2017)

Papers in preparation and to be submitted before publication of the main analyses:

1. Cohort profile (submitted 17/9/2019)
2. Tobacco survey (re-submitted 15/10/2019)
3. Comparison between the mortality data received from ZAGS and MIAC (in progress)
4. Exposure assessment and assignment (the UralAsbest JEM) (in progress)