April 2022

**Protocol - EPHOR Work Package 8.3: Impact Assessment**

**Matt Gittins, Luke Munford, Ioannis Basinas, Martie van Tongeren, ….??**

**University of Manchester**

# Contents Page

[Contents Page 3](#_Toc97305527)

[List of Tables 5](#_Toc97305528)

[List of Figures 7](#_Toc97305529)

[Glossary 8](#_Toc97305530)

[1 Brief Background/Introduction 9](#_Toc97305531)

[1.1 Aims/Objectives 10](#_Toc97305532)

[1.1.1 Original Objectives - WP8 10](#_Toc97305533)

[1.1.2 Original Description of work and role of partners 11](#_Toc97305534)

[1.1.3 OBJECTIVE/AIMS – Specific Work Package 8.3 12](#_Toc97305535)

[2 Methods 13](#_Toc97305536)

[2.1 Background Case studies/Literature Review 13](#_Toc97305537)

[2.2 Simulation Study 17](#_Toc97305538)

[2.3 Study Population 17](#_Toc97305539)

[2.4 Defining the Outcome of Interest 17](#_Toc97305540)

[2.4.1 Primary Outcome – Life expectancy of Lung Cancer 17](#_Toc97305541)

[2.5 Explanatory/Independent Variables 21](#_Toc97305542)

[2.5.1 Time invariant exposure covariate(s) 21](#_Toc97305543)

[2.5.2 Time varying exposure covariate(s) 22](#_Toc97305544)

[2.6 Permutational Algorithms – Simulating time to event with time-varying exposure histories. 24](#_Toc97305545)

[2.6.1 Permutational Algorithms with rejection sampling 24](#_Toc97305546)

[2.7 Defining the covariate exposure histories 26](#_Toc97305547)

[2.7.1 Defining Exposure – Respirable Crystalline Silica (RCS) 26](#_Toc97305548)

[2.7.2 Lagged Exposure–Response – ‘Decaying’ Risk and Latency Periods 29](#_Toc97305549)

[2.7.3 Co-Exposure(s) definition – The Working Life Exposome? 30](#_Toc97305550)

[2.7.4 Non-working life confounders 33](#_Toc97305551)

[2.7.5 Exposure Intervention 35](#_Toc97305552)

[2.8 Developing the Exposome-outcome framework 37](#_Toc97305553)

[2.8.1 The basic single exposure-outcome model 37](#_Toc97305554)

[2.8.2 Introduction of time-invariant confounding 39](#_Toc97305555)

[2.8.3 Introduction of additional time-varying work-related co-exposures (without additional confounding) 41](#_Toc97305556)

[2.8.4 Introduction of co-exposures (with correlation structures) 44](#_Toc97305557)

[2.8.5 Introduction of (independent) co-exposures with additional non-work-related confounding 50](#_Toc97305558)

[2.8.6 Introduction of (correlated) co-exposures with additional non-work-related confounding 53](#_Toc97305559)

[2.8.7 Introducing a single moderating (independent) co-exposure 59](#_Toc97305560)

[2.8.8 Introducing a single moderating (correlated) co-exposure 62](#_Toc97305561)

[3 Analysis methods 70](#_Toc97305562)

[3.1 Defining the data generation (Random number generation) 70](#_Toc97305563)

[3.2 Estimating the Health Impact of the Intervention 71](#_Toc97305564)

[3.3 Summarising results, and assessing performance of Health Interventions, comparing within and between scenarios 72](#_Toc97305565)

[3.3.1 Summarising each intervention effect across the simulations 72](#_Toc97305566)

[3.3.2 Assessing the performance of each intervention effect 73](#_Toc97305567)

[3.4 Defining the Sample size & Simulation No. 73](#_Toc97305568)

[4 Results 75](#_Toc97305569)

[5 Discussion/Conclusion 76](#_Toc97305570)

[5.1 Conclusion 76](#_Toc97305571)

[6 References 77](#_Toc97305572)

# List of Tables

[Table 1 – Correlation Structure of Work-related co-exposures 32](#_Toc97305573)

[Table 2 - Scenarios to be simulated for Single Time-Varying Exposure (Fixed Work Duration) 38](#_Toc97305574)

[Table 3 - Scenarios to be simulated for Single Time-Invariant Exposure (Random Work Duration) with additional non-working life confounding factors 40](#_Toc97305575)

[Table 4 - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional independent work exposure (asbestos) 42](#_Toc97305576)

[Table 5 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional independent work exposure (asbestos, diesel, wood dust) 43](#_Toc97305577)

[Table 6 - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional moderately correlated work exposure (asbestos) 45](#_Toc97305578)

[Table 7 - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional strongly correlated work exposure (asbestos) 46](#_Toc97305579)

[Table 8 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional moderately correlated work exposure (asbestos, diesel, wood dust) 47](#_Toc97305580)

[Table 9 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional strongly correlated work exposure (asbestos, diesel, wood dust) 48](#_Toc97305581)

[Table 10 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional correlated work exposures (asbestos, diesel, wood dust) with a bespoke structure 49](#_Toc97305582)

[Table 11 - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional independent work exposure (asbestos) repeated with additional for non-work confounders. 51](#_Toc97305583)

[Table 12 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional independent work exposure (asbestos, diesel, wood dust) repeated with additional for non-work confounders 52](#_Toc97305584)

[Table 13 - Scenarios to be simulated for Single Exposure (Random Work Duration) with single additional moderately correlated work exposure (asbestos) repeated to include additional non-working confounders. 54](#_Toc97305585)

[Table 14 - Scenarios to be simulated for Single Exposure (Random Work Duration) with single additional strongly correlated work exposure (asbestos) repeated to include additional non-working confounders 55](#_Toc97305586)

[Table 15 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional moderately correlated work exposures (asbestos, diesel, wood dust) repeated to include additional non-working confounders 56](#_Toc97305587)

[Table 16 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional strongly correlated work exposures (asbestos, diesel, wood dust) repeated to include additional non-working confounders 57](#_Toc97305588)

[Table 17 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional work exposures (asbestos, diesel, wood dust) with bespoke correlation structure and repeated to include additional non-working confounders 58](#_Toc97305589)

[Table 18 - Scenarios to be simulated for Single Exposure (Random Work Duration) with single additional independent work exposure (asbestos) with additional for non-work confounders where the co-exposure ‘asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 60](#_Toc97305590)

[Table 19 - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional independent work exposure (asbestos, diesel, wood dust) with additional for non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 61](#_Toc97305591)

[Table 20 - Scenarios to be simulated for Single Exposure (Random Work Duration) a single additional moderately correlated work exposure (asbestos) with additional for non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 63](#_Toc97305592)

[Table 21 - Scenarios to be simulated for Single Exposure (Random Work Duration) a single additional strongly correlated work exposure (asbestos) with additional for non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 64](#_Toc97305593)

[Table 22 - Scenarios to be simulated for Single Exposure (Random Work Duration) a multiple additional moderately correlated work exposure (asbestos, diesel, Wood dust) with additional non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 65](#_Toc97305594)

[Table 23 - Scenarios to be simulated for Single Exposure (Random Work Duration) multiple additional strongly correlated work exposure (asbestos, diesel, Wood dust) with additional non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 67](#_Toc97305595)

[Table 24 - Scenarios to be simulated for Single Exposure (Random Work Duration) multiple additional ‘bespoke’ correlated work exposure (asbestos, diesel, wood dust) with additional non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%. 69](#_Toc97305596)

# List of Figures

[Figure 1 – A DAG representing the basic model, single exposure single outcome relationship 37](#_Toc97305597)

[Figure 2 – A DAG representing the basic model, single exposure single outcome relationship with additional confounding 39](#_Toc97305598)

[Figure 3 – A DAG representing the basic model, multi-independent exposure - outcome relationship without additional confounding 41](#_Toc97305599)

[Figure 4 – A DAG representing the basic model, multi-correlated exposure - outcome relationship without additional confounding 44](#_Toc97305600)

[Figure 5 – A DAG representing the multi-independent exposure(s) - outcome relationship with additional confounding 50](#_Toc97305601)

[Figure 6 – A DAG representing the correlated exposure(s) - outcome relationship with additional confounding 53](#_Toc97305602)

[Figure 7 – A DAG representing the basic model, multi-independent exposure - outcome relationship with additional confounding and a single moderating co-exposure. 59](#_Toc97305603)

[Figure 8 – A DAG representing the, multi- correlated exposure(s) - outcome relationship with additional confounding and a single moderating co-exposure. 62](#_Toc97305604)

# Brief Background/Introduction

Exposures at the workplace contribute to many non-communicable diseases (NCDs) with a similar magnitude as urban air pollution or obesity. Given the associated societal and economic (2-6% GDP) pressure, ensuring a healthy work environment is a strategic goal for the European Commission. Demographic changes (aging workforce, female workers) and the rapidly changing nature of work with respect to secure employment and migration, are posing additional challenges. We define the working-life exposome as all occupational and related non-occupational factors (general and socio-economic environment, lifestyle, behaviour). Taking a working-life exposome approach will help address these challenges by providing better insights in how complex working-life exposures are related to NCDs, for vulnerable groups (female, migrant, insecure job workers) or life stages. The working-life exposome is in its infancy and new approaches and methods are needed. In EPHOR a consortium of exposure, health and data scientists and technology developers will develop a working-life exposome toolbox, with stakeholder involvement. The toolbox will make available to scientists, policy makers and occupational health practitioners: 1) innovative methods for collection, storage, and interpretation of more complete and individual level working life exposome data; 2) better knowledge on how the working life exposome relates to NCDs, including complex interactions, vulnerability, biological pathways and early signs of health damage, by uniquely combining large-scale pooling of existing cohorts with focused case studies; 3) models for assessing the economic and societal impact of working life exposures. EPHOR will lay the groundwork for evidence-based and cost-effective preventive actions to reduce the burden of NCDs as a result of the working-life exposome. Thereby, health, wellbeing and productivity of the EU population will be improved and the burden on the EU health care systems reduced. EPHOR is part of the European Human Exposome Network comprised of 9 projects selected from this same call.

## Aims/Objectives

### Original Objectives - WP8

WP8 focusses on the development of health and economic impact assessment of working life exposome data that will provide knowledge on complex interactions and disease mechanisms. WP8 will use cohort data from WP5 and exposure prevalence from the application of the dynamic EuroJEM from WP2 for simulations during method development and the results of WP5, 6 & 7 for demonstration of the methods.

The objective is to bring the exposome concept to health impact assessment by developing methods to incorporate life course and co-exposures to multiple risks. Specific objectives are:

* Incorporate the exposome concept (complex exposure scenarios with increased multiple exposures, internal as well as external, and early markers of effects along mechanistic biological pathways) and working-life (working-life specific health metrics) into the models currently used to determine health impact (T 8.1, 8.2)
* Incorporate new knowledge obtained during the EPHOR project to estimate health impact for several hypothetical health-based interventions in the workplace (T8.3)
* Develop guidelines for health impact assessment to be included in the toolbox (T8.4)

### Original Description of work and role of partners

Task 8.1

*Exposome burden of disease model (UU, UNIMAN, TNO, IOM, FIOH) (M1-24)*

Conceptual models will be developed for exposome burden of disease for several health outcomes that are of relevance for working-life health (and based on studies included in WP5) describing the interlinkages between the various internal and external exposures and confounding factors and with health outcomes, including markers along the AOPs. The conceptual model will be visualised highlighting the relative importance of exposure metrics and exposure-response pathways based on existing evidence from the peer-reviewed literature. The conceptual model will be used to develop the complex modelling of interacting risk factors and interventions in Task 8.3.

Task 8.2

*Working-life specific health metrics for impact assessment (FIOH, UNIMAN, IOM) (M1-12)*

A detailed and systematic literature review will be carried out to establish current knowledge on the link between exposures, socioeconomic indicators (e.g. educational level, social class, income) and working-life expectancy. Working-life specific health metrics will subsequently be used within Task 8.3 to estimate health impact.

Task 8.3

*Exposome health impact assessment (UNIMAN, UU, IOM, FIOH, TNO, STAMI, KI) (M12-56)*

A simulated longitudinal population cohort will be developed based on empirical data from WP2 and WP5 to estimate the impact of workplace interventions. The exposure(s), demographic and socioeconomic profiles of the simulated datasets cohorts will be based on data from WP2 and WP5 and information obtained from the wide range of published literature.

The conceptual model(s) developed in Task 8.1 will be used to implement initially relatively simple exposure scenarios and risk functions, evolving into more complex exposome profiles with various correlation structures and risk functions, involving multiple exposures and confounders, such as socioeconomic status as well as interactions between the risk factors. In particular, correlations between exposures and socioeconomic factors in relation to disease outcomes will be studied. A set of intervention scenarios will be developed, aimed to reduce future health burden and calculate the expected health impacts over a 20-60 year time period, accounting for regional and population differences. Scenarios will be developed with the benefit of stakeholder consultations organised in collaboration with WP10. Such scenarios would also look at changing exposures and risks over the life course, extending the working age, precarious work (e.g. people who do multiple temporary jobs), migratory work, etc. In addition to estimating the impact of interventions on clinical health outcomes, models will be developed for impact assessment using intermediate markers of exposure and incorporating concepts from the adverse outcome pathways. Such approaches would enable combination of health impact modelling with quantitative or qualitative evaluations of interventions, in relation to external exposures. This work will build on the mechanistic biological pathway modelling developed in T6.3 and T7.4. Task 8.3 will inform the development of guidelines in Task 8.4, in particular providing guidance on when the inclusion of complex exposure scenarios will result in more accurate estimates of burden of disease/health impact (and when conventional impact assessment models suffice).

Task 8.4

*Tools and guidance for impact assessment (UNIMAN, UU, IOM, FIOH, TNO) (M36-56)*

Guidance and tools will be developed (feed into toolbox WP9) to incorporate exposome complexity in health impact assessment and determine criteria to assess conditions when taking account of whether exposome complexity is of benefit and efficient in estimating the health impact of interventions. Guidelines and criteria will be developed based on the purpose of the health impact assessment, knowledge available on risk functions and complexity of the exposure scenario, to determine the method most appropriate for the health impact assessment required.

### OBJECTIVE/AIMS – Specific Work Package 8.3

A simulated longitudinal population cohort will be developed based on empirical data from WP2 and 5 to estimate the impact of workplace interventions. The exposure, demographic and socioeconomic profiles of the simulated datasets will be based on data from WP2 and 5 and information obtained from the literature.

This will be split into two main tasks

1. To better understand how a single exposure-outcome relationship is influenced by changes in the individuals exposome. We simulate a known ‘single’ exposure – outcome relationship and then manipulate characteristics assumed to be representative of the persons exposome.
2. To better understand how the consequences of an exposure intervention can be influenced by the exposome. We introduce a set of exposure interventions with differing characteristics, whilst manipulating both characteristics of the exposome and characteristics of the intervention.

# Methods

The following outlines a protocol designed to develop a simulated longitudinal cohort that can be used to understand the impact of workplace ‘exposure’ interventions on a health outcome under varying exposome and intervention characteristics. Through the use of simulation studies, we will be able to gain insight under a variety of scenarios into the influence of an intervention on population level outcomes. Scenarios that we can manipulate and control without the interference of unknown factors. The simulated datasets will be based on the conceptional models developed in WP8.1, the review of Working Life Expectancy developed in WP8.2, and the real-world empirical studies outlining work related exposures that affect work and health. The real-world studies will be based around the following exposure-outcome relations: Respirable Crystalline Silica (RCS) and Lung Cancer incidence. These will help inform the underlying structure and characteristics of our simulated data. In particular they will help define our ‘known truths’ i.e. here our definition of the ‘true’ effect of exposure on outcome. We aim for this work to be representative of real-world events, with estimates and conclusions of a representative true effect.

## Background Case studies/Literature Review

The following outlines a brief literature review of current work looking at Silica and Lung Cancer. This information will be used to simulate a representative cohort of construction workers and their exposome characteristics.

**Literature review/Case Study - Silica and Lung Cancer**

Silica (SiO2) comprises part of the earth’s crust and thereby is one of the most common minerals in existence. It can exist in both an amorphous and crystalline form, of which the latter is the most stable and important. The respirable fraction of this crystalline form has been associated with a broad range of health symptoms including silicosis, respiratory disorders and disease and cancer.

In occupational settings, RCS exposure can commonly occur in scenarios where earth or earth products are processed or disturbed such as during mining, movement and cultivation of soul/earth (e.g. tunnelling, agriculture), when processing mined materials, producing or handling concrete, mortar etc, when sandblasting, in construction, in foundries as well as when manufacturing glass or ceramic products.

There is a breadth of epidemiological evidence related to the health effects of RCS and particularly in relation to lung cancer. Several meta-analysis have been published on the topic whereas in 1997 and more recently in 2018 IARC evaluated the carcinogenicity of RCS in the form of quartz or chistobalite (the most common forms of RCS).1 Following their latest evaluation IARC experts concluded that there was sufficient evidence available that RCS in the forms of quartz or cristobalite dust causes lung cancer in humans and thereby classified RCS as a Group 1 carcinogen.

In their evaluation IARC reviewed studies on with the focus on exposure response relationship and included 10 cohort studies and 17 case-control studies, as well as 8 meta-analyses, of which though only one consider exposure-response relationships in its framework. From the cohorts included, 2 concerned exposure during work related to the diatomaceous earth industry, 4 during ore mining, 2 during quarrying, and 2 during the processing of sand and gravel. From those studies Checkoway et al.2 and Rice et al.3 studies the association between cumulative exposure to silica and lung cancer among 2342 workers in a diatomaceous earth mining and processing facility in California initially by applying analysis with exposure treated both as a categorical and continuous variable. Their analyses with a continuous exposure variable returned a significant positive association between cumulative silica exposure and lung cancer with a RR (95CI%) of 1.06 (1.01 – 1.11) in the first analysis and 1.64 for the re-analysis following implementation of a 10 year lag.

Steenland and Brown,4 used quantitative estimates of cumulative exposure based on particle counts to study the association between silica and lung cancer in a population of more than 3000 US miners. The authors found no obvious evidence for an exposure–response relationship with lung cancer mortality. This is in contrast to the results of a cohort of 2209 South African gold miners by Hnizdo and Sluis-Cremer published a little earlier.5 In this cohort the authors calculated the cumulative respirable surface area years for the participants and in models with a continuous a exposure there was a significant association with the incidence of lung cancer (RR=1.02; 95%CI = 1.01-1.04). Similarly, a cohort of 724 Sardinian miners with silicosis using quantitative estimates of cumulative exposure to RCS and radon categorised in 4 intensity groups also showed the potential presence of an association between RCS and lung cancer mortality with SMR between 1.25 and 1.55 . However, there was no evidence for an exposure-response relationship and tests for trends remained non-significant.6

Similar results were obtained in a study of 440 German stone and quarry workers but among Attfield & Costello analysed quantitative RCS dust measurements undertaken throughout a study of 5414 granite quarry and shed workers and estimated the cumulative exposure of the participants.7 They used the derived estimates to study the association with lung cancer mortality and observed a clear trend of an increased risk of lung cancer mortality with increasing cumulative respirable exposure. Risk estimates ranged between 1.18 and 2.6 in analysis utilising 7 groups of exposure (0.25,0.5,1.0,1.5, 2.0, 3.0, 6.0) versus the non-exposed.

In another cohort involving 4626 industrial sand workers employed between 1960 and 1988 in 18 sand and gravel companies, Steenland & Sanderson also employed quantitative estimates of exposure and reported indications for an exposure-response relationship with lung cancer mortality.8 Estimates of Risk were 0.78, 1.51 and 1.57 for those subjects with >0.10-0.51, >0.51-1.28, and >1.28 mg-yrs/m3 of exposure compared with those with cumulative exposure ranging between >0-0.10 who were the reference. Brown & Rushton also studies the association of cumulative RCS to lung cancer in a cohort of workers from the sand industry.9 10 In this case though, the RR appeared to increase in the first two quartiles (RR =1.24 and 2.42, respectively), but fell below 1.0 in the highest quartile (RR=0.88). As a result no trends in the exposure-response relationship were observed.

Among case-control studies Reid and Sluis-Cremer in a study of 159 miners and 318 aged matched controls nested within a larger cohort of South African gold miners observed an OR (95% CI) of 1.19 (0.97-1.70) when analysing estimates of the participants cumulative RCS exposure as a continuous variable.11 Similar evidence for a positive exposure-resposne relationship were also reported in another study of South African gold miners including 78 cases and 386 controls.12 The authors observed an increasing trend with increased cumulative exposure significant for the highest exposed category compared to the lowest. The derived ORs were 1.83 (0.8-4.1), 1.85 (0.8-4.3) and 3.19 (1.3-7.6) for the mediate (2.7-4.3 mg-yr/m3), intermediate (4.4-6.3 mg-yr/m3) and high (>6.3 mg-yr/m3) exposure group compared to the lowest (0<2.7 mg-yr/m3), respectively.

Cherry et al., in a study of 52 males cases and 197 male controls employed in the ceramics (i.e. pottery, sandstone, refractory) industry used continuous quantitative estimates of cumulative RCS dust exposure (μg-yr/m3) and of average intensity to study the exposure response relationship with lung cancer.13 The authors observed an OR of 1.01 (0.85-1.19) in the analysis using cumulative exposure and of 1.67 (1.13-2.47) in the analysis using the average intensity concentrations.

Similar positive trends in exposure response relationships were also observed in two case-control studies of workers in the sand and gravel industry. First Steenland and Sanderson in a study of 75 cases and controls nested within the previously mentioned cohort reported evidence of exposure–response using quartiles of cumulative exposure (p = 0.04), but the evidence were much stronger when average intensity was used with OR estimates ranging between 0.92 and 2.26 (p = 0.003).8 The ORs for the cumulative exposure when lagged 15 years ranged between 1.35 to 2.0. Similarly, MacDonnald et al., in a study of 105 cases matched with up to 2 controls each on the basis of age and date of first employment reported OR of 1.10 , 1.77, and 2.64 for the cumulative RCS exposures ranging between 700 – 1800, 1800-4500, >4500 ug-yr/m3 compared with lowest exposed who had levels of cumulative exposure <700 ug-years/m3.14 Further evidence and similar results on the exposure response relationship between silica exposure and lung cancer were also provided in case control studies among Chinese iron and steel workers and US aluminium foundry workers.15 16

Steenland et al. performed a nested case-control analysis of a pooled study comprised from ten cohorts representing various countries and industries.17 The analysis comprised of 992 cases and 100 controls per case matched upon race, sex, date of birth and study. Indices of exposure employed included quantitative estimates of average and cumulative RCS exposure at a normal and log scale with and without lags. The authors reported highly significant trends with lung cancer risk (P < 0.0001) for all cumulative indices employed. Reported OR for the cumulative RCS exposure (unlagged) ranged between 1.0 – and 1.6.

Another meta-analytical study reporting results on the exposure-response relationship between was published by Lacasse et al.,.18 Based on 10 studies (4 cohort and 6 case–control studies) having quantitative RCS measurements of exposure and including adjustments for smoking the authors observed an increasing risk of lung cancer with increased cumulative RCS exposure. RRs corresponding to increases of 1.0 and 6 mg/m3 per year were estimated to be 1.22 (CI: 1.01–1.47) and 1.84 (CI: 1.48–2.28), respectively.

Finally, m recently Shabhazi et al., published a meta-analysis looking on the relationship between silica and the risk of developing lung cancer in studies published as recently as 2020.18 Nineteen studies from 14 countries were included. Using random effect analysis with linear and cubic spline effects the authors observed a significant linear association between silica exposure and risk of lung cancer with a RR of 1.25 and a 95% CI between 1.03 and 1.49, which suggested an increase of 25% in risk of lung cancer per unit of increase in cumulative exposure to silica.

## Simulation Study

The following outlines our predefined definitions and methodology to simulate data representative of the construction industry, its exposome, and health outcome lung cancer incidence. The aim is to represent a hypothetically true working life exposome-outcome relationship. We will then simulate an exposure/exposome intervention and its subsequent influence on the health outcome. We begin here by defining the health outcomes of interest. The standard simulation methodology for time-to-event data will be outlined, before explaining why it is not suitable here and the alternative methodology (permutational algorithms). We outline the ‘working life exposure’ and ‘non-exposure’ related factors, their interrelationship (our hypothetical exposome), and their relationship to our predefined outcome. This may include single or multiple exposures along with key confounding factors, and the health outcome of interest based in the conceptual model. Finally, we will describe the proposed exposure intervention in terms of its size and scope.

## Study Population

We aim to simulate a study population that is representative of a longitudinal cohort study in which the risk of an exposome-outcome relationship is being investigated. Here this will be representative of a cohort study of those in the construction industry that are at increased risk of lung cancer due to exposure to silica and its common co-exposures.

## Defining the Outcome of Interest

### Primary Outcome – Life expectancy of Lung Cancer

Time from initiation of exposure to lung cancer diagnosis will be the simulated outcome event of interest. Lung cancer is the second most common cancer in men and women. Cancer Research UK indicates a life-time risk of developing Lung cancer within the general population is estimated to be 1 in 13 for men and 1 in 15 for women.19 It is rare for lung cancer to be diagnosed in those younger than 40, with the average age of diagnosis being in the mid to late 60s.

#### Simulating Time to Lung Cancer Diagnosis

We assume here that time to diagnosis follows a time-to-event (survival) random variable T, where the event of interest is diagnosis of lung cancer. Here we generate a population in which we know the working life histories for all simulated subjects. We will then simulate a time to diagnosis using a Monte Carlo simulation method, in which a random number is generated from a uniform [0,1] distribution. The value drawn is then mapped to a corresponding value drawn from an inverse cumulative distribution function of a specified probability density function.20 21 The random variable T is associated cumulative distribution function, F(T), where survival times can be simulated from a distribution such that:

F ∼ U(0, 1)

To simulate each observation, we draw from the uniform distribution, where

u ∼ U(0, 1),

and simply substitute and solve for t, F(t) = u and hence,

t = F −1 (u)

To model the effect of the covariates on the hazard of the occurrence of the outcome (i.e. permanent removal from the work force), the conventional method is the Cox proportional model with fixed or time-invariant covariates and is defined as,

h(t | x) = h0(t) exp(β ′ x)

where  β the vector of regression coefficients and h0(t) is the baseline hazard function of the outcome at time t occurring for those subjects with the vector of covariates x = 0. The survival function of the above model is

S(t | x) = exp( − H0(t) exp(β ′ x)),

where H0(t) is the cumulative baseline hazard function, defined as

The given survival function is 1 – F(t) the cumulative distribution function of the event times under the Cox proportional hazards model is:

F(t | x) = 1 − exp( − H0(t) exp(β ′ x)).

The survival time, T, can be generated by,

where u ∼ U(0,1) denotes the standard uniform distribution and H0 is the baseline hazard function i.e the hazard function when x equals zero.20 22

To translate the regression effects from a hazard function to survival time the baseline hazard function needs to be constant, with most simulation studies employing the exponential, Weibull, or Gompertz distribution to simulate a realistic baseline hazard function as they satisfy the proportional hazard function.20 23 The Inverse cumulative baseline hazard function for the Weibull distribution is defined as:

The survival time (i.e WLE) can then be expressed as:

Where λ\*exp(-βx) is the scale parameter, and ν represents the shape parameter. If v=1 then the hazard function collapses down to the exponential. If v is greater than 1 the hazard function increases, between 0 and 1 it decreases monotonically.

The corresponding survival time for the Gompertz distribution can be expressed as:

Where if α the Gompertz shape parameter is equal to 0 the hazard function once again collapses to the exponential. If α<0 the hazard function decreases, and if α>0 the hazard function increases. The scale parameter λ\*exp(-βx).

#### Defining the shape and scale parameters

The choice of distribution, and corresponding scale and shape parameters defined to generate a representative set of survival times in the simulation study that are similar to observed survival times. We can relate the expected value of the Gompertz model to the time to diagnosis of our representative cohort. The appropriate parameter values for the Gompertz model cannot be calculated directly from a representative cohort. Instead we approximate from the survival function from an extreme value distribution. The hazard function of the extreme value distribution is identical to that of the Gompertz distribution if t>=0.20 Here for the extreme value distribution the mean E(T) and variance Var(T) of T can be defined as:

, and

Where π is the constant pi = 3.14159, and γ is Euler’s constant at 0.5772.20

To then simulate time to event data all we require is a **representative estimate of the mean and variance for time from first exposure to time to lung cancer diagnosis**. Further investigation of the conceptual model (e.g. exposures/confounders) can be explored by manipulation of the explanatory covariates X in shape parameter λ\*exp(-βx).

## Explanatory/Independent Variables

The section outlines our definitions of the key variables used to explain our simulated time to event data. These will be based on the literature outlined in section 2.1, and will include characteristics and distributional properties of our exposome i.e. the individual exposures present in the multiple exposure concept. Starting with a single ‘primary’ exposure, we will expand to multiple additional co-exposures. In addition to their distributional properties, we will pre-define their known relationships with the outcome. An additional set of confounding factors and their characteristics will also be pre-defined.

For the purpose of the analysis, we define occupational exposure as the concentration of the substance or agent in the breathing zone of the workers during the working day. The total amount of a substance or agent that a person is exposed over a certain period of time is called the “cumulative exposure” and it is most frequently estimated as the annual average exposure received in a job over the duration of the job (in years) summed for all jobs that the individual held within the period of interest. This is most simply expressed by the following formula:

*Cumulative exp* = *Σ(Ti x Ci)*

where Ti is the period in years that a person worked in job *i*, and Ci is the average exposure intensity (usually daily) that he was exposed while in this job. This formula can further be extended for example by including the frequency of exposure (e.g. days per year) that one experienced per year. Typically during estimation the average daily exposure is assumed to vary across years within the same job with intensity generally being reduced as the year’s progress. This annual decline is typically a result of improvements in technology, changes in legislation and/or the underlying processes within the job and when exposure measurements are available can be estimated by formal statistical analysis. Typical annual declines in aerosol exposures are reported to be in the range of 1 to 10% although instance of annual increases have also reported for certain job/industry and substance combinations.24 The estimated cumulative exposure can be included either as a continuous covariate in analysis or, in the most usual approach, it is used to rank cohort participants as no, low, medium or high exposed. For the development of these exposure categories frequently the quartiles or tertiles of the distribution of estimated continuous cumulative exposure in the population are used.

### Time invariant exposure covariate(s)

Occupational exposures can vary considerably over time. In this simulation study we will ultimately aim to represent exposure as a cumulative total exposure that increases as exposure period increases, similar to the type of exposures experienced in construction workers over their working life. This would be in the form of a time varying exposure i.e. total exposure received at work changes (increases) during the time the participant is at work. Initially we may want to describe the underlying survival hazard function in the context of a time invariant exposure, where the exposure is simulated to be fixed over the course of the exposure period. Here those in the simulated study population may be assigned a ‘representative’ cumulative total exposure for their working life, which is then used to define them as being in a fixed categorical group such as low, medium, or high exposure throughout their working life.

The survival time for the Gompertz distribution assuming a time-invariant exposure as described in Section 2.4.1 was expressed as:

Where if α is the Gompertz shape parameter and λ\*exp(-βx) is the Gompertz scale parameter. The explanatory covariates X present in scale parameter λ\*exp(-βx) are constant across time (i.e. time-invariant). Factors that were measured at baseline, or in our definition of time-invariant exposure, are those that are constant across the follow up time and remain unchanged.

### Time varying exposure covariate(s)

The explanatory covariates X present in shape parameter λ\*exp(-βx), have so far been considered here as constant across time (i.e. time-invariant). Here we would want to simulate scenarios where a time-varying covariate is present i.e. the value recorded in the variable changes during exposure. This is particularly important for working exposures which will increase over working life and the cumulative dose will influence the risk of our lung cancer diagnosis.

**Continuous time-varying cumulative exposure**

The time-invariant simulated data scenario can be extended to include a time-varying covariate.25 Here the cumulative exposure is a continuous covariate which increases at a constant rate over time with a constant increase to the risk. The x covariates included in the shape parameter under exp(-βx) represent our fixed baseline covariates. To include a time-varying z covariate with its own corresponding coefficient θ. The cumulative hazard function is extended:

Where z(t) represents the function of the time-varying covariate z across time t. Assuming the Gompertz distribution for event times, we simulate event times T under the time-varying covariate scenarios that might represent changing exposure status. Here z(t) becomes a continuous variable that is proportional to t such that z(t) = et, where e is the constant exposure increase that is greater than 0, and t is the time point where et becomes the cumulative exposure at time point t. This would represent subjects who are exposed to an approximately fixed dose each year, that over time accumulates.

The corresponding survival time for the Gompertz distribution with a time-varying cumulative dose can be expressed as:

Where, as before, α is the shape parameter, λ\*exp(βx) is the scale parameter, and u is a random draw from the uniform distribution.25

## Permutational Algorithms – Simulating time to event with time-varying exposure histories.

The change in exposure amount and the corresponding change in exposure effect has so far been assumed to be constant across time. Subjects would be randomly assigned an annual amount of exposure experienced, and the cumulative exposure effect is then based on the number of years worked to date multiplied by the constant increase. This would also assume that increase risk per year experienced by the subject is maintained over time. In reality a health outcome may be associated with exposure that may change each year, and the effect of exposure in the past may be delayed (latency period) or may decay over time since the exposure occurred. These concepts have been proposed both within the conceptual model in work package 8.1, and debated and applied in epidemiological literature for cancer for some time,26 27 but also more recently to acute conditions associated with the effects of ambient temperature and air pollution.28 29

### Permutational Algorithms with rejection sampling

The methods proposed so far rely on an inverted survival function to generate survival times with a annual exposure that is constant i.e. each year the exposure remains the same. Inverting a survival function with time-varying exposure amount cannot be described with a parametric function, or defined for the whole exposure time period.30 Permutation Algorithms (PA) are able to generate event and censoring times conditional on a set of covariates that may also include time-varying annual exposure time-dependent.30 31 The PA in its originally proposed form is computationally intensive when a large number of events need to be generated, however previous work has shown that a rejection sampling approach maintains unbiased estimates with comparable variance whilst reducing computational time.30

The steps involved for simulating time to event using PA with rejection sampling are as follows:

1. Generate a set of N event times from a pre-specified marginal distribution that represents the distribution of events in the entire study population regardless of the covariates.
2. Generate a set of censor times based on a pre-specified marginal distribution.
3. For each individual define ‘time’ as the minimum of the event time or the censor time, and the indicator of an event vs censor as those whose event time is less than or equal to the censor time. Sort in order of individuals ‘time to event/censor’.
4. Generate for each N a covariate matrices. Within each matrix the row represents a follow up time point where for example 1 might be first year of work, 2 second year, etc. Each column represents either a fixed in time covariates (e.g. gender), or a time dependent covariate (e.g. change in exposure amount).
5. Starting from the smallest ‘time to event/censor’, randomly assign time to event and indicator of event/censor to a vector of the covariate values using the rejection sampling method.
   1. Sample a ‘vector of covariate values’ from all N ‘vectors of covariate values’ at the ‘time to event/censor’ based on equal probabilities 1 / number of vectors still unassigned (note N in first round, N-1 in second round, etc)
   2. Draw a random value U from uniform distribution between 0 and 1 U[0,1].
   3. Compute the hazard ratio associated with vector of covariate values for the sampled vector
   4. If the U is less than or equal to the hazard ratio divided by the largest hazard ratio for all vectors of covariates within the time point, then match the time to event and the covariate of vectors. Otherwise restart at step a.
   5. Once matched the subject and vector is assigned the time to event/censor and the corresponding matrix prior to the time point is the subjects exposure history. The vectors of exposure history post the time point are then dropped.
   6. The matched matrix of covariates and subjects are then removed, and the process repeats with the remaining set of subjects and matrices of covariates.

#### Defining the N Event/Censoring times

The cohort is representative of constructions workers, in which not everyone will develop lung cancer. To incorporate censoring (i.e. those deemed to not get lung cancer during follow up), we simulate for each simulated subject a set of event times and a second set of censoring times. The minimum time is then the observed survival time, and an indicator of the event (i.e. lung cancer or not) generated. We propose to simulate our event times and our censor times based on draws from a two Gompertz distributions such that 10% of the sample subjects will be identified as having lung cancer. It worth noting that it there is evidence to suggest that the accuracy of PA increases with decreasing censor rates, but the variance of distributed events may be overestimated.30 31 The Gompertz distribution will be representative of the time to cancer diagnosis and censor times (i.e. the alive at last follow up time). To then simulate time to event data all we require is a **representative estimate of the mean and variance for time from first exposure to time to lung cancer diagnosis/censor**.

## Defining the covariate exposure histories

To investigate scenarios where exposure intensity and time since exposure are important, i.e. the exposure histories of a subject, we will generate a time-varying lagged exposure profile for each simulated subject.28 29 For each simulated subject we generate a series of exposures et where t represents the year the participant was exposed such that time t = 1 is the first year of work. This will follow the structure described in the PA method such that the column represents the exposure and row represents the year. Each year the annual exposure is generated as a random exposure event within an exposure intensity range defined in section 2.7.1 and by any proposed intervention. To represent the lagged exposure, additional columns will be generated to represent the exposure occurring in the l year prior to the year t i.e. exposure history occurring in t-l years prior year t.29

The exposure–lag–response associations are then defined by functions representing the exposure-response and the lag-response.29 The exposure-response relationship will be set to be linear with defined intensity outlined in 2.7.1. The lag-response functions are defined by simple mathematical functions that represent our assumptions of a decaying risk and a latency period.

### Defining Exposure – Respirable Crystalline Silica (RCS)

Here primary exposure of interest will be representative of Respirable Crystalline Silica (RCS) and will be assumed to follow a linear exposure-response relationship. The α shape parameter, and the λ scale parameter were defined previously in section 2.4.1. In addition, definitions are required of the simulated subject exposure histories i.e. the vector of x covariates and β a vector of regression coefficients associated with each covariate representing exposure, one of which will represent the primary exposure in this case RCS. The βexposure here represents our known truth i.e. the effect that we define to be the true unit increase in annual-exposure effect occurring within the year of exposure. Note, annual exposure is required for the simulation methodology and not cumulative exposure.

#### Defining the exposure structure

Occupational exposures are commonly measured on a daily, full-shift (i.e. 8-hr) basis. These measurements are consequently typically used to develop further exposure metrics that may be biologically relevant to the health outcome of interest. For chronic diseases including cancers the most relevant exposure metric is cumulative exposure during the duration of employment. The distribution of this continuous statistical covariate, is often subsequently used to re-categorised the population at hand as exposed vs unexposed, or Low, Medium, or High exposed. To fully understand the exposure-outcome relationship under the influence of changing exposome scenarios we will focus on the cumulative exposure experienced by simulated subjects representative of the construction industry. To simulate this under varying exposure histories we need to understand the annual average exposure experienced and its corresponding effect on outcome.

The cumulative RCS exposure can be defined as the annual exposure concentration for a particular role multiplied by the duration of years worked in that role. The current EU Directive on Carcinogens and Mutagens at Work implemented recommended a limit of 0.1 mg/m3 exposure to RCS dust.32 Exposure to RCS during construction work is reported to differ depending on the period of interest with in principle levels of exposure being much lower in recent years primarily as result of changes in technology, legislation and exposure controls. For example, Dutch construction workers in 2011 were reported to be exposed to RCS levels with a Geometric Mean (GM) level of 0.1 mg/m3 and a Geometric standard deviation (GSD) of 3.84.33 However, RCS levels in construction have been reported to decline by approximately 10% on an annual basis and current (GM) levels of RCS exposure among Danish construction workers were reported to be much lower ranging between 0.005 and 0.018 mg/m3.24 34 35 Although that the average exposures across the industry appear to be low considerable differences between occupations exists. Earlier research characterising the variability of RCS exposure among construction workers reported the between workers variance component to be 3 folds larger than the within workers variance components ( 3.2 vs 1,0), which corresponds to a 3 orders of a magnitude variation in the measured exposure levels between workers– i.e. a ratio between the 97.5 and 2.5 percentiles of the distribution of the log-transformed corresponding variance component equal to 1,100.36 37

For our simulations we will base our exposure estimations on the previously mentioned exposure results among Dutch construction workers in 2011.33 We will assume GM levels of exposure to follow a log normal distribution and to decline annually by 10% in order to calculate average annual exposure levels for 5 years interval periods starting from 1960 and until 2020 (Table 1). These exposure estimates will be used to replicate annual average exposures among the participants (assuming a 240 working days exposure) and derive with the total cumulative life-time exposure of each participant. For example, If a participant initiated work in construction in 1970 and worked for 40 years these estimations would result in an cumulative life-time exposure of 70.3 mg/m3\*years.

**Table 1.** Estimated average Geometric mean levels of RCS exposure from 1960 to 2020 in the construction industry.Estimates are based on the results of van Deurssen et al (ref) assuming a 10% annual decline in exposure.

|  |  |  |  |
| --- | --- | --- | --- |
| **Time period** | **start year** | **stop year** | **Average GM RCS level (mg/m3)** |
| 1 | 1960 | 1965 | 16.759 |
| 2 | 1965 | 1970 | 9.896 |
| 3 | 1970 | 1975 | 5.844 |
| 4 | 1975 | 1980 | 3.451 |
| 5 | 1980 | 1985 | 2.038 |
| 6 | 1985 | 1990 | 1.203 |
| 7 | 1990 | 1995 | 0.710 |
| 8 | 1995 | 2000 | 0.420 |
| 9 | 2000 | 2005 | 0.248 |
| 10 | 2005 | 2010 | 0.146 |
| 11 | 2010 | 2015 | 0.086 |
| 12 | 2015 | 2020 | 0.051 |

Exposure duration will be simulated for each participant under three scenarios a flat 20 years representing a job role change, 45 years similar job role, or a random exposure length with mean exposure of 35 years (s.d 5 years).38 Once the exposure period has ended all simulated subjects will be considered as zero additional exposure.

#### Exposure-Response effect - the ‘known truth’

The exposure-outcome effect is our ‘known truth’. Here we will assume a linear exposure-response relationship is present. Traditionally simulation studies considered multiple effect sizes that are representative of small, medium, and large exposure effects observed. This should give us insight into how changes in the exposome, and influence of intervention on the true exposure level over varying magnitude of increased risk and study sizes.

As outlined in section 2.1 typical hazard ratios for studies investigating cumulative silica exposure have ranged between 1.02 and 1.40 (based on 95% C.I.s) per 1 mg/m3 year unit increase in total cumulative RCS exposure. These sizes of effects are also confirmed by a recent meta-analysis, which assessed the exposure-response relationship between occupational silica exposure and lung cancer among nineteen studies published between 1991 and 2020.18 Study estimates were grouped and analysed according to six levels of average annual silica exposure: ≤ 0.49 mg/m3, 0.50–0.99 mg/m3, 1.00–1.99 mg/m3, 2.00–2.99 mg/m3, 3.00–3.99 mg/m3, ≥ 4.00 mg/m3 using random effect models. Linear and cubic splines were also implemented to study further the exposure response relationship. The results of the categorised analysis suggested a clear positive exposure response relationship with a pooled risk estimate of 1.27 (95% CI=1.19-1.36) whereas the results of the splines were similar suggesting a linear positive trend with a 25% increase per cumulative unit of exposure (RR of 1.25, 95% CI = 1.03-1.49). Based on those findings, and given the hazard ratio produced in survival analysis is a relative change in the hazard we will define a small, medium and large increase in risk to be **5%, 25%, and 45%.**

### Lagged Exposure–Response – ‘Decaying’ Risk and Latency Periods

#### Decaying Risk

As explored in Work Package 8.1 subjects with the same cumulative exposure but different temporal exposure patterns can be associated with differing disease risks. To simulate a decaying cumulative exposure, we include a set of additional covariates to the exposure history of the simulated subject that represent the annual exposure measures associated with lagged decaying effect preceding each year t.

el=e(t-l)\*2^(-l/d)

where el = decay-adjusted annual exposure associated with lth year prior to the current exposure year t, e(t-l) = original annual exposure occurring at year t-l, d = decay half-life in years. For the purposes of the simulation study we will simulate up to 20 years of decaying risk prior to t, and will explore the influence of a decaying risk under no decaying risk is present, **a 5 year, and a 10 year half-life decay**.

#### Latency Period

Occupational exposures are commonly associated with ill-health events, particularly cancer, that contain latency periods i.e. a delay between first exposure and disease development. Latently periods of 5 or 10 years are thought common, depending on the cancer of interest. We can define a period where simulated subjects are exposed but see no directly related increase in risk (i.e. essentially unexposed), before an increase in risk occurs. For a cumulative total exposure this can be simulated by adjusting the lagged annual exposure variables used to simulate the exposure-outcome relationship such that exposure for the latency period is set at zero, before increasing at the level observed at the beginning of the lag period.

el = 0 if l<=tl

el= e(t-l) if l>tl

Where annual exposure for each t years is et, el is the annual exposure that occurred in the previous lth year, and tl is the length of the latency period. For the purposes of the simulation study to see the influence of a lag period we will simulate scenarios that assume no latency period is present, and a period is of **5 years, and a period of 10 years**.

### Co-Exposure(s) definition – The Working Life Exposome?

The working life part of the exposome is a group of interrelating exposures experienced during a person’s working life that are thought to modify their risk of a health event. In construction this could relate to any secondary common chemical exposures present on a construction site such as asbestos, wood dust, diesel engine and other combustion fumes, which include polycyclic aromatic hydrocarbons (PAHs), solvents, chromium, nickel, wood dust, and particulate matter (PM10/2.5). These co-exposures commonly occur in construction and may co-exist with our proposed main exposure RCS in that they are often produced under similar processes and so are highly correlated. To explore the influence of working life co-exposures we propose to focus on simulating three additional chemical exposures asbestos, diesel engine exhaust fumes, and wood dust.

#### The Co-exposures (Asbestos, Diesel fumes, Wood dust) structural properties

The three co-exposures will be simulated in a similar method to the main exposure of interest under the same assumptions for time trends in exposure (i.e. 10% decrease in exposure levels per year) and will represent a cumulative exposure over their working life. In terms of exposure duration, we will assume that if simulated subjects are exposed to our primary exposure ‘RCS then they are also being exposed to our secondary exposure’s asbestos, diesel, and wood dust.

***Asbestos:*** The HSE recommend a control limit for asbestos is 0.6 asbestos fibres per cubic centimetre of air (0.6 f/ml), measured over a ten-minute period.39 Recently published results from an exposure database containing more than 9000 measurements of asbestos exposure collected between 1971 and 1997 reported Danish construction workers to be exposed during abatement activities performed between 1981 and 1987 to asbestos levels that ranged between 0.02 and 93 f/cm3.40 The same study reported great reductions in average exposures to have occurred between the same period. These declining trends in exposure following the ban of asbestos use in Europe were verified in recently published measurement results collected among Italian construction workers – levels of exposure) in the period between 1996 and 2013 averaged (GM) at **0.007 f/cm3**, with a GSD of 5.82.41 Assuming a 10% annual decline in exposure and a career of 40 years starting in1970 this would result in an average annual exposure of 0.056 f/cm3.

Concerning associated risks, Lenters et al., examined the exposure-response relationship between asbestos exposure and lung cancer in a meta-analysis of 19 epidemiological studies.42 Using random effect models they observed a meta-KL (× 100) of 0.13 (95% CIs: 0.04, 0.22) with an intercept of 1.47 representing a RR of 1.66 (95% CI: 1.53, 1.79) per 100 fiber-years/ml.

***Diesel****:* Lewne et al., reported diesel fumes in the form of Inhalable Elemental Carbon (EC) among Swedish construction workers to average between 4 ug/m3 for outdoor construction work and 87 ug/m3 during tunnel construction.43 Levels of respirable exposure among workers involved in tunnel construction work in the area London were reported to have a GM level of 18 ug/m3 with a GSD of 1.0 which was generally similar to the levels of exposure reported among Canadian underground workers recently (GM= 13.2 ug/m3; GSD=1.83).44 45 In the same study among Canadian construction workers measurements of EC during below grade and above ground work had GM (GSD) levels of 3.56 ug/m3 (1.94) and 1.49 ug/m3 (1.75), respectively. This study was performed between 2018 and 2020 and the measurements has an overall GM of **3.71 ug/m3** with a GSD of 3.32.45 Accounting for the latter results among Canadian workers and assuming again a 10% annual decline in exposure, a 40 years career with exposure with a beginning in 1970 we can estimate that the average annual exposure for the workers of 151 ug/m3 and a total cumulative exposure estimate for the period of 6058 ug/m3 \*years.

Vermeulen et al. in a meta-regression analysis of three large occupational cohort studies estimated an lnRR of 0.00098 (95% CI: 0.00055, 0.0014) for lung cancer mortality with each 1-μg/m3-year increase in cumulative EC exposure. 46

**Wood dust**: The exposure of construction workers to wood dust is reported to be highly variable depending on the job and activity of the workers involved. Dutch carpenters in construction have previously been reported to be exposed to mean (GM) time-weighted average wood dust levels of 3.3 mg/m3 with a GSD of 2.1.47 These estimates were based on 44 personal measurements performed in 2002 in workers across 13 building projects. This is comparable to personal levels reported for UK construction joiners performed near the same period (median = 2.6 mg/m3, interquartile range=0.6-3.3 mg/m3).48 Assuming an average exposure at this level (i.e. 2.6 mg/m3) during the year of 2000, an annual declining trend of 10% in exposure, and a 40 years working career starting in 1970 we can estimate a total cumulative exposure to wood dust of 573.5 mg/m3\*years, corresponding to an annual average level of 14.4 mg/m3 for the complete period.

Rearding risks, Hanckock et al. performed a meta-analysis of 85 publications that assess the relationship between wood dust and lung cancer.49 The authors observed an increased risk for developing lung cancer among studies that directly assessed wood dust exposure (RR 1.21, 95% CI 1.05 to 1.39, n=33). Valieres et al., also studied the risk of lung cancer by occupational exposure to wood dust in two Canadian population based case-control studies.50 In one of the involved studies, using controls comprising patients of other cancers the authors reported an OR of 1.4 (95% CI = 1.0 -2.0) for substantial exposure compared to non exposure. In the other, this time with population controls, substantial exposure to wood dust was associated with an OR of 1.7 ((5% CI = 1.1 – 2.7). Substantial exposure was defined as exposure to medium or high concentrations, during more than 5% of the work week for 5 years or more.

**Correlation Structure of the Work-related exposures**

Work-related exposures such as RCS, asbestos, diesel engine exhaust, and wood dust are likely to have a complex correlation structure. Strong correlations may influence any single exposure-outcome relationship, and any effect of an intervention that might have been implemented. To investigate the influence of correlated multiple exposures we will gradually introduce additional exposures alongside RCS, with increasing strength of correlation. We will begin by introducing a single additional exposure (asbestos) with an independent relationship, before increasing the correlation structure to 0.1 and 0.5 i.e. a medium and high strength correlation. We then include a third and fourth exposure (Diesel, and wood dust). Again, all correlation between the four exposures will initially be independent, before medium, and then high strength correlations are added. Finally, a model that includes a mix of correlations between the multiple exposures will be fitted. The correlation structures proposed are outlined further in Table 1.

Table – Correlation Structure of Work-related co-exposures

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Model |  | Working Life Exposures | | | |
|  |  | Silica | Asbestos | Diesel | Wood dust |
| Single Co-exposure | Asbestos | 0 |  |  |  |
| Asbestos | 0.1 |  |  |  |
| Asbestos | 0.5 |  |  |  |
|  |  |  |  |  |  |
| Multiple Co-exposures | Silica | 1 |  |  |  |
| Asbestos | 0 | 1 |  |  |
| Diesel | 0 | 0 | 1 |  |
| PM2.5 | 0 | 0 | 0 | 1 |
|  |  |  |  |  |
| Silica | 1 |  |  |  |
| Asbestos | 0.1 | 1 |  |  |
| Diesel | 0.1 | 0.1 | 1 |  |
| Wood dust | 0.1 | 0.1 | 0.1 | 1 |
|  |  |  |  |  |
| Silica | 1 |  |  |  |
| Asbestos | 0.5 | 1 |  |  |
| Diesel | 0.5 | 0.5 | 1 |  |
| Wood dust | 0.5 | 0.5 | 0.5 | 1 |
|  |  |  |  |  |  |
| Bespoke Structure | Silica | 1 |  |  |  |
| Asbestos | 0.5 | 1 |  |  |
| Diesel | 0.1 | 0.5 | 1 |  |
| Wood dust | 0.2 | 0.1 | 0.5 | 1 |

#### Exposure-outcome effect - the ‘known truth’

In order to reduce the complexity and focus on the main exposure effect the pre-defined relationship between each co-exposure and the main outcome will be set a constant increase in risk for each exposure per annual unit increase of annual exposure (see section 2.7.3).

#### Latency Period

To reduce the complexity and number of scenarios here we will focus on two scenarios related to the latency periods a zero latency period and a 5 year latency period for all co-exposures.

#### Decaying Risk

Similarly to reduce the number of scenarios here we will focus on two decay frequencies related to a zero decay period and a 5 year decay period for all co-exposures.

### Non-working life confounders

In addition to working exposures there are several ‘non-working confounding’ factors present in the exposome concept. These are factors related to an increased risk that are not directly related to work but are more common in a particular industry. These might include, but are not exclusive to, gender, birth cohort, and smoking level. Our simulated cohorts will be representative of the common sample structure associated with these factors for construction workers.

**Age at entry:** Simulatedsubjects are all assumed to enter the workforce in their 20s with a uniform distribution to baseline age. We will assume here that age at entry itself has no influence on the subjects lung cancer risk outside of that defined by the baseline risk or their exposure profile.

**Gender:** The percentage of females in the construction industry as reported by the Office of National Statistics has been consistent since the 1990s at approximately 10% of constructions workers.51 Cancer Research UK indicates that between 2016-18 the current age standardised lung cancer rates for females were 70.1 and males 90.6 per 100,000.52 Indicating a relative risk of 1.29 for males compared to females. We will assume this is consistent within our simulated construction cohort and set the hazard ratio for males vs females as 1.30.

**Birth Cohort:** Assessments of age standardised lung cancer incidence in the general population has indicated a declining trend since the early 1990s, with some evidence suggesting declining trends since the 1970s.53 54 This is likely to be due to declining trends in smoking, however the Health and Safety Executive estimates that future occupational related cancers related to RCS and asbestos are expected to drop by 50% and 90% respectively by 2060.55 To reflect these trends we will simulate a birth cohort effect to represent four groups of workers entering work during 10 year periods since 1970s. We will assume that entry into the construction sector has been constant (i.e. an even split for each birth cohort) and that each successive 10 year period will assume a 10% reduction in risk.

**Smoking:** Is a significant risk factor for lung cancer and a common confounder in any research study. In cross sectional surveys describing smoking in construction workers, some 36% report being current smokers. We would expect that a significant proportion are former smokers and so our data will assume that 30% are current smokers of which 15% are heavy smokers and 15% light smokers, 30% are then former smokers, and the remaining 40% are never smokers. Systematic reviews of current smokers and former smokers compared to non-smokers indicate relative risks of 7.3 (95% C.I. 4.9,10.9) and 3.14 (2.45,4.03) for males separately (results were similar for females only) respectively. We will assume that being a current heavy smoker holds the greatest risk. The hazard ratios associated with former smokers , current light, and current heavy compared to the non-smokers will be set as 3.0, 8.0. and 12.0 respectively.

### Exposure Intervention

Reducing or preventing work-related ill-health due to occupational related exposures is achieved through reduction or elimination of the exposure experienced by the employee. A recent systematic review of occupational intervention studies occurring between 1960 and 2019 and targeting exposure to chemical and biological agents,56 classified interventions into one of four intervention types:

* A control measure such as a ventilation system,
* behaviour/education/training program,
* policy e.g. smoking ban or limits on exposure,
* or Personal Protective Equipment (PPE).

The majority of the studies reviewed (73%) reported an intervention outcome effect related to a reduction in the exposure. These influences were observed to vary between 5/6% for educational programs, to 30% for control measures, to 80% policy interventions specifically bans. Though this was also observed to vary with characteristics of the population and intervention understudy.

Here, we wish to better understand the influence of potential exposure interventions on a lung cancer outcome. To do so within each simulation scenario outlined we will simulate an exposure intervention based on the appropriate intervention scenarios outlined in the systematic review, These will be defined as the following set of interventions:

* The annual exposure level is reduced by 30%.
* The maximum value of the annual exposure level is reduced by 1/3rd (i.e. simulating imposed limits)
* These two interventions will be repeated for all exposures, and the primary exposure ‘silica’ only i.e. that the intervention does not influence the secondary working life exposures, and for all exposures i.e. both the primary exposures and all secondary exposures.
* We will simulate the intervention occurring at a particular time point i.e. to simulate an intervention occurring at a set time/calendar year. This will simulate a new policy intervention occurring within a workforce where a percentage has already been exposed, or a proportion of their working life has periods with different levels of exposure. Using our Birth Cohorts as a guide (1970+) we will set the intervention to occur in 2000, and 2010 to see how our proposed interventions implemented at an earlier time point vs a later time point will influence the health outcome observed.

In each case we will then compare the influence of the exposure with and without the intervention, on lung cancer outcome events.

## Developing the Exposome-outcome framework

The following outlines the planned progression of increasingly complex scenarios. We plan to develop gradually from a simple exposure-outcome model to the complex multi-exposure, multi factor - outcome model. To describe these increasingly complex relationships we employ the graphical tool to represent the hypothetical causal relationships, a directed acyclic graphs (DAGs).57 58 A concept that has been developed to help describe casual relationships, understanding confounders, and potential sources of bias in exposure–outcome relationships.57 In a DAG, a causal relationship is represented by an arrow, or path, between the variables, illustrating the direction of cause to effect.

Note, within each of the scenarios proposed below we will be exploring the influence of a set of health interventions (see Section 2.7.5) on the proposed health outcome (see Section 3.2) under the changing exposome characteristics. Therefore each simulation will include an assessment of the no-intervention health outcome and the corresponding health outcome when each of the interventions area applied.

### The basic single exposure-outcome model

To investigate the complex exposome – outcome relationship, we first need to confirm that a) our simulations are accurately portraying the single exposure – outcome relationship, and b) that we understand how the underlying exposure characteristic can influence our proposed health outcome. We therefore begin by developing the single exposome-outcome relationship under no additional influence, as described in Figure 1.

Figure – A DAG representing the basic model, single exposure single outcome relationship

Exposure

Outcome

Table 2, outlines the definition of each scenario we propose to explore under the single time-varying cumulative exposure to RCS. The exposure period (i.e. the full work life period) is defined to be initially a fixed 40 year exposure period for all before being randomly assigned. In each case, we initially simulate adjusting for characteristics related to cohort study sample size and effect size, this in part to confirm we are correctly observing our known truths. We then manipulate our exposure-outcome relationship to include a latency period of 5 years and 10 years, and a decaying risk with a half-life also 5 and 10 years.

Table - Scenarios to be simulated for Single Time-Varying Exposure (Fixed Work Duration)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | |
|  | **1000** | **10000** | **100000** | **5%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** |
| **Fixed 40 years exposure period** | 1.001 | | | X | X | X |  |  |  |  |
| 1.002 | | | X | X | X | X |  |  |  |
| 1.003 | | | X | X | X |  | X |  |  |
| 1.004 | | | X | X | X |  |  | X |  |
| 1.005 | | | X | X | X |  |  |  | X |
| 1.006 | | | X | X | X | X |  | X |  |
| 1.007 | | | X | X | X | X |  |  | X |
| 1.008 | | | X | X | X |  | X | X |  |
| 1.009 | | | X | X | X |  | X |  | X |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 1.101 | | | X | X | X |  |  |  |  |
| 1.102 | | | X | X | X | X |  |  |  |
| 1.103 | | | X | X | X |  | X |  |  |
| 1.104 | | | X | X | X |  |  | X |  |
| 1.105 | | | X | X | X |  |  |  | X |
| 1.106 | | | X | X | X | X |  | X |  |
| 1.107 | | | X | X | X | X |  |  | X |
| 1.108 | | | X | X | X |  | X | X |  |
| 1.109 | | | X | X | X |  | X |  | X |

### Introduction of time-invariant confounding

Studies of occupational exposure assessments are observational in nature with significant amounts of confounding. To explore the influence of confounding factors such as gender, ethnicity, or smoking we introduce confounding factors not directly associated with the working life. Here these will be Gender, Birth cohort, and Smoking and will be assumed to be time-invariant and representative of the construction industry being simulated.

Figure – A DAG representing the basic model, single exposure single outcome relationship with additional confounding

Exposure

Outcome

Confounder(s)

Table 3 repeats the simulation scenarios outlined in Table 2 with the addition of all three time-invariant confounding factors present.

Table - Scenarios to be simulated for Single Time-Invariant Exposure (Random Work Duration) with additional non-working life confounding factors

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Non-Working Life Confounders** |
|  | **1000** | **10000** | **100000** | **5%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** |  |
| **Fixed 40 years exposure period** | 1.201 | | | X | X | X |  |  |  |  | x |
| 1.202 | | | X | X | X | X |  |  |  | x |
| 1.203 | | | X | X | X |  | X |  |  | x |
| 1.204 | | | X | X | X |  |  | X |  | x |
| 1.205 | | | X | X | X |  |  |  | X | x |
| 1.206 | | | X | X | X | X |  | X |  | x |
| 1.207 | | | X | X | X | X |  |  | X | x |
| 1.208 | | | X | X | X |  | X | X |  | x |
| 1.209 | | | X | X | X |  | X |  | X | x |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 1.301 | | | X | X | X |  |  |  |  | x |
| 1.302 | | | X | X | X | X |  |  |  | x |
| 1.303 | | | X | X | X |  | X |  |  | x |
| 1.304 | | | X | X | X |  |  | X |  | x |
| 1.305 | | | X | X | X |  |  |  | X | x |
| 1.306 | | | X | X | X | X |  | X |  | x |
| 1.307 | | | X | X | X | X |  |  | X | x |
| 1.308 | | | X | X | X |  | X | X |  | x |
| 1.309 | | | X | X | X |  | X |  | X | x |

### Introduction of additional time-varying work-related co-exposures (without additional confounding)

Within the exposome concept, the employee is assumed to experience multiple exposures during the working life, the additional influence of these exposures and their interrelationship are of significant concern. Here we have defined three additional co-exposures asbestos, diesel, and Wood dust. As with the main exposure, RCS, we assume that they are time-varying and are modelled as the cumulative dose received during the complete working life. Here we assume that each co-exposure is independent of each other, in other words a high RCS exposure does not necessarily indicate a high asbestos exposure as well.

Figure – A DAG representing the basic model, multi-independent exposure - outcome relationship without additional confounding

Exposure

Outcome

Co-Exposure(s)

In order to reduce and focus the number of scenarios being proposed, we now assume that the working life period is randomly assigned. Table 4 outlines the scenarios proposed assuming a single additional time-varying independent co-exposure, asbestos. Asbestos is assumed here to have a fixed known effect estimate of 5% per 100 fibre-years/ml increase in total cumulative exposure. Additional scenarios assume that the single co-exposure is defined as having a 5 year latency period and a 5 year half-life decay similar to the primary exposure. Table 5 repeats the scenarios outlined in Table 4 however we include all three proposed co-exposures asbestos, diesel and wood dust. In each case the known effect will be a 5% increase in a unit of 100 fibre-years/ml, 100 ug/m3\*years and 1 mg/m3\*years, respectively, and the latency and decay characteristics held constant across all three co-exposures.

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional independent work exposure (asbestos)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Indep Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **5%** | **5%** | **20%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 2.001 | | | X | X | X |  |  |  |  | x |  |  |
| 2.002 | | | X | X | X | X |  |  |  | x |  |  |
| 2.003 | | | X | X | X |  | X |  |  | x |  |  |
| 2.004 | | | X | X | X |  |  | X |  | x |  |  |
| 2.005 | | | X | X | X |  |  |  | X | x |  |  |
| 2.006 | | | X | X | X | X |  | X |  | x |  |  |
| 2.007 | | | X | X | X | X |  |  | X | x |  |  |
| 2.008 | | | X | X | X |  | X | X |  | x |  |  |
| 2.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 2.101 | | | X | X | X |  |  |  |  | x | x |  |
| 2.102 | | | X | X | X | X |  |  |  | x | x |  |
| 2.103 | | | X | X | X |  | X |  |  | x | x |  |
| 2.104 | | | X | X | X |  |  | X |  | x | x |  |
| 2.105 | | | X | X | X |  |  |  | X | x | x |  |
| 2.106 | | | X | X | X | X |  | X |  | x | x |  |
| 2.107 | | | X | X | X | X |  |  | X | x | x |  |
| 2.108 | | | X | X | X |  | X | X |  | x | x |  |
| 2.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 2.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 2.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 2.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 2.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 2.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 2.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 2.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 2.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 2.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 2.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 2.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 2.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 2.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 2.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 2.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 2.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 2.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 2.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional independent work exposure (asbestos, diesel, wood dust)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Multi-Indep Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **5%** | **5%** | **20%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 3.001 | | | X | X | X |  |  |  |  | x |  |  |
| 3.002 | | | X | X | X | X |  |  |  | x |  |  |
| 3.003 | | | X | X | X |  | X |  |  | x |  |  |
| 3.004 | | | X | X | X |  |  | X |  | x |  |  |
| 3.005 | | | X | X | X |  |  |  | X | x |  |  |
| 3.006 | | | X | X | X | X |  | X |  | x |  |  |
| 3.007 | | | X | X | X | X |  |  | X | x |  |  |
| 3.008 | | | X | X | X |  | X | X |  | x |  |  |
| 3.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 3.101 | | | X | X | X |  |  |  |  | x | x |  |
| 3.102 | | | X | X | X | X |  |  |  | x | x |  |
| 3.103 | | | X | X | X |  | X |  |  | x | x |  |
| 3.104 | | | X | X | X |  |  | X |  | x | x |  |
| 3.105 | | | X | X | X |  |  |  | X | x | x |  |
| 3.106 | | | X | X | X | X |  | X |  | x | x |  |
| 3.107 | | | X | X | X | X |  |  | X | x | x |  |
| 3.108 | | | X | X | X |  | X | X |  | x | x |  |
| 3.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 3.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 3.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 3.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 3.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 3.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 3.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 3.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 3.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 3.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 3.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 3.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 3.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 3.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 3.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 3.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 3.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 3.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 3.309 | | | X | X | X |  | X |  | X | x | x | x |

### Introduction of co-exposures (with correlation structures)

Working life co-exposures rarely can be assumed to be independent. We therefore repeat the simulated scenarios assuming co-exposures are correlated to varying degrees of strength.

Figure – A DAG representing the basic model, multi-correlated exposure - outcome relationship without additional confounding

Exposure

Outcome

Co-Exposure(s)

Table 6 and Table 7, repeat the simulations presented in Table 4 in that an additional single co-exposure asbestos is assumed to be present, however this co-exposure is assumed here to be moderately correlated (0.1) and strongly correlated (0.5), respectively. Table 8 and Table 9 repeat Table 5 to include all three co-exposures asbestos, diesel, and wood dust. Again, we assume a constant correlation structure is present across all exposures relating a moderate and strong correlation respectively. As constant correlation structure is unlikely, we repeat our simulations (Table 10) assuming a more bespoke correlation structure across the four exposures. See section 2.7.3 for more details on the bespoke correlation structure proposed.

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional moderately correlated work exposure (asbestos)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos corr=0.1** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 4.001 | | | X | X | X |  |  |  |  | x |  |  |
| 4.002 | | | X | X | X | X |  |  |  | x |  |  |
| 4.003 | | | X | X | X |  | X |  |  | x |  |  |
| 4.004 | | | X | X | X |  |  | X |  | x |  |  |
| 4.005 | | | X | X | X |  |  |  | X | x |  |  |
| 4.006 | | | X | X | X | X |  | X |  | x |  |  |
| 4.007 | | | X | X | X | X |  |  | X | x |  |  |
| 4.008 | | | X | X | X |  | X | X |  | x |  |  |
| 4.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 4.101 | | | X | X | X |  |  |  |  | x | x |  |
| 4.102 | | | X | X | X | X |  |  |  | x | x |  |
| 4.103 | | | X | X | X |  | X |  |  | x | x |  |
| 4.104 | | | X | X | X |  |  | X |  | x | x |  |
| 4.105 | | | X | X | X |  |  |  | X | x | x |  |
| 4.106 | | | X | X | X | X |  | X |  | x | x |  |
| 4.107 | | | X | X | X | X |  |  | X | x | x |  |
| 4.108 | | | X | X | X |  | X | X |  | x | x |  |
| 4.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 4.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 4.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 4.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 4.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 4.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 4.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 4.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 4.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 4.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 4.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 4.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 4.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 4.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 4.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 4.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 4.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 4.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 4.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional strongly correlated work exposure (asbestos)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos corr=0.5** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 5.001 | | | X | X | X |  |  |  |  | x |  |  |
| 5.002 | | | X | X | X | X |  |  |  | x |  |  |
| 5.003 | | | X | X | X |  | X |  |  | x |  |  |
| 5.004 | | | X | X | X |  |  | X |  | x |  |  |
| 5.005 | | | X | X | X |  |  |  | X | x |  |  |
| 5.006 | | | X | X | X | X |  | X |  | x |  |  |
| 5.007 | | | X | X | X | X |  |  | X | x |  |  |
| 5.008 | | | X | X | X |  | X | X |  | x |  |  |
| 5.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 5.101 | | | X | X | X |  |  |  |  | x | x |  |
| 5.102 | | | X | X | X | X |  |  |  | x | x |  |
| 5.103 | | | X | X | X |  | X |  |  | x | x |  |
| 5.104 | | | X | X | X |  |  | X |  | x | x |  |
| 5.105 | | | X | X | X |  |  |  | X | x | x |  |
| 5.106 | | | X | X | X | X |  | X |  | x | x |  |
| 5.107 | | | X | X | X | X |  |  | X | x | x |  |
| 5.108 | | | X | X | X |  | X | X |  | x | x |  |
| 5.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 5.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 5.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 5.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 5.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 5.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 5.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 5.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 5.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 5.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 5.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 5.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 5.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 5.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 5.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 5.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 5.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 5.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 5.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional moderately correlated work exposure (asbestos, diesel, wood dust)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=0.1** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 6.001 | | | X | X | X |  |  |  |  | x |  |  |
| 6.002 | | | X | X | X | X |  |  |  | x |  |  |
| 6.003 | | | X | X | X |  | X |  |  | x |  |  |
| 6.004 | | | X | X | X |  |  | X |  | x |  |  |
| 6.005 | | | X | X | X |  |  |  | X | x |  |  |
| 6.006 | | | X | X | X | X |  | X |  | x |  |  |
| 6.007 | | | X | X | X | X |  |  | X | x |  |  |
| 6.008 | | | X | X | X |  | X | X |  | x |  |  |
| 6.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 6.101 | | | X | X | X |  |  |  |  | x | x |  |
| 6.102 | | | X | X | X | X |  |  |  | x | x |  |
| 6.103 | | | X | X | X |  | X |  |  | x | x |  |
| 6.104 | | | X | X | X |  |  | X |  | x | x |  |
| 6.105 | | | X | X | X |  |  |  | X | x | x |  |
| 6.106 | | | X | X | X | X |  | X |  | x | x |  |
| 6.107 | | | X | X | X | X |  |  | X | x | x |  |
| 6.108 | | | X | X | X |  | X | X |  | x | x |  |
| 6.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 6.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 6.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 6.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 6.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 6.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 6.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 6.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 6.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 6.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 6.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 6.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 6.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 6.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 6.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 6.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 6.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 6.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 6.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional strongly correlated work exposure (asbestos, diesel, wood dust)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=0.5** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 7.001 | | | X | X | X |  |  |  |  | x |  |  |
| 7.002 | | | X | X | X | X |  |  |  | x |  |  |
| 7.003 | | | X | X | X |  | X |  |  | x |  |  |
| 7.004 | | | X | X | X |  |  | X |  | x |  |  |
| 7.005 | | | X | X | X |  |  |  | X | x |  |  |
| 7.006 | | | X | X | X | X |  | X |  | x |  |  |
| 7.007 | | | X | X | X | X |  |  | X | x |  |  |
| 7.008 | | | X | X | X |  | X | X |  | x |  |  |
| 7.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 7.101 | | | X | X | X |  |  |  |  | x | x |  |
| 7.102 | | | X | X | X | X |  |  |  | x | x |  |
| 7.103 | | | X | X | X |  | X |  |  | x | x |  |
| 7.104 | | | X | X | X |  |  | X |  | x | x |  |
| 7.105 | | | X | X | X |  |  |  | X | x | x |  |
| 7.106 | | | X | X | X | X |  | X |  | x | x |  |
| 7.107 | | | X | X | X | X |  |  | X | x | x |  |
| 7.108 | | | X | X | X |  | X | X |  | x | x |  |
| 7.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 7.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 7.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 7.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 7.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 7.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 7.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 7.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 7.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 7.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 7.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 7.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 7.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 7.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 7.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 7.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 7.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 7.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 7.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional correlated work exposures (asbestos, diesel, wood dust) with a bespoke structure

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=bespoke** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 8.001 | | | X | X | X |  |  |  |  | x |  |  |
| 8.002 | | | X | X | X | X |  |  |  | x |  |  |
| 8.003 | | | X | X | X |  | X |  |  | x |  |  |
| 8.004 | | | X | X | X |  |  | X |  | x |  |  |
| 8.005 | | | X | X | X |  |  |  | X | x |  |  |
| 8.006 | | | X | X | X | X |  | X |  | x |  |  |
| 8.007 | | | X | X | X | X |  |  | X | x |  |  |
| 8.008 | | | X | X | X |  | X | X |  | x |  |  |
| 8.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 8.101 | | | X | X | X |  |  |  |  | x | x |  |
| 8.102 | | | X | X | X | X |  |  |  | x | x |  |
| 8.103 | | | X | X | X |  | X |  |  | x | x |  |
| 8.104 | | | X | X | X |  |  | X |  | x | x |  |
| 8.105 | | | X | X | X |  |  |  | X | x | x |  |
| 8.106 | | | X | X | X | X |  | X |  | x | x |  |
| 8.107 | | | X | X | X | X |  |  | X | x | x |  |
| 8.108 | | | X | X | X |  | X | X |  | x | x |  |
| 8.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 8.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 8.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 8.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 8.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 8.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 8.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 8.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 8.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 8.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 8.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 8.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 8.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 8.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 8.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 8.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 8.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 8.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 8.309 | | | X | X | X |  | X |  | X | x | x | x |

### Introduction of (independent) co-exposures with additional non-work-related confounding

The exposome concept encompasses multiple interrelated work-related exposures and multiple non-work-related characteristics. Here we incorporate both the time-varying co-exposures and the time invariant confounding factors. Initially we assume that the time-varying co-exposures are independent of each other and the primary exposure RCS.

Figure – A DAG representing the multi-independent exposure(s) - outcome relationship with additional confounding

Exposure

Outcome

Co-Exposure(s)

Confounders

Table 11 repeats the scenarios assuming a single additional time-varying independent co-exposure asbestos however here we also include our time-invariant confounders: gender, birth cohort, and smoking. Asbestos is again assumed to have a fixed known effect estimate of 5% per unit increase in total cumulative exposure, and additional scenarios assume a 5 year latency period and a 5 year half-life decay. Table 12 repeats but here includes all three additional co-exposures asbestos, diesel and wood dust 5. Again the known effect will be a 5% increase in all co-exposures and the latency and decay characteristics held constant across all three co-exposures.

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional independent work exposure (asbestos) repeated with additional for non-work confounders.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Indep Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 9.001 | | | X | X | X |  |  |  |  | x |  |  |
| 9.002 | | | X | X | X | X |  |  |  | x |  |  |
| 9.003 | | | X | X | X |  | X |  |  | x |  |  |
| 9.004 | | | X | X | X |  |  | X |  | x |  |  |
| 9.005 | | | X | X | X |  |  |  | X | x |  |  |
| 9.006 | | | X | X | X | X |  | X |  | x |  |  |
| 9.007 | | | X | X | X | X |  |  | X | x |  |  |
| 9.008 | | | X | X | X |  | X | X |  | x |  |  |
| 9.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 9.101 | | | X | X | X |  |  |  |  | x | x |  |
| 9.102 | | | X | X | X | X |  |  |  | x | x |  |
| 9.103 | | | X | X | X |  | X |  |  | x | x |  |
| 9.104 | | | X | X | X |  |  | X |  | x | x |  |
| 9.105 | | | X | X | X |  |  |  | X | x | x |  |
| 9.106 | | | X | X | X | X |  | X |  | x | x |  |
| 9.107 | | | X | X | X | X |  |  | X | x | x |  |
| 9.108 | | | X | X | X |  | X | X |  | x | x |  |
| 9.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 9.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 9.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 9.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 9.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 9.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 9.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 9.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 9.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 9.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 9.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 9.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 9.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 9.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 9.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 9.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 9.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 9.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 9.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional independent work exposure (asbestos, diesel, wood dust) repeated with additional for non-work confounders

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Multi-Indep Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos|Diesel|Wood dust** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 10.001 | | | X | X | X |  |  |  |  | x |  |  |
| 10.002 | | | X | X | X | X |  |  |  | x |  |  |
| 10.003 | | | X | X | X |  | X |  |  | x |  |  |
| 10.004 | | | X | X | X |  |  | X |  | x |  |  |
| 10.005 | | | X | X | X |  |  |  | X | x |  |  |
| 10.006 | | | X | X | X | X |  | X |  | x |  |  |
| 10.007 | | | X | X | X | X |  |  | X | x |  |  |
| 10.008 | | | X | X | X |  | X | X |  | x |  |  |
| 10.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 10.101 | | | X | X | X |  |  |  |  | x | x |  |
| 10.102 | | | X | X | X | X |  |  |  | x | x |  |
| 10.103 | | | X | X | X |  | X |  |  | x | x |  |
| 10.104 | | | X | X | X |  |  | X |  | x | x |  |
| 10.105 | | | X | X | X |  |  |  | X | x | x |  |
| 10.106 | | | X | X | X | X |  | X |  | x | x |  |
| 10.107 | | | X | X | X | X |  |  | X | x | x |  |
| 10.108 | | | X | X | X |  | X | X |  | x | x |  |
| 10.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 10.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 10.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 10.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 10.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 10.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 10.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 10.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 10.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 10.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 10.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 10.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 10.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 10.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 10.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 10.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 10.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 10.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 10.309 | | | X | X | X |  | X |  | X | x | x | x |

### Introduction of (correlated) co-exposures with additional non-work-related confounding

We then assume that the time-varying co-exposures are correlated with each other and the primary exposure RCS with varying degrees of strength.

Figure – A DAG representing the correlated exposure(s) - outcome relationship with additional confounding

Exposure

Outcome

Co-Exposure(s)

Confounders

Table 13 Table 14 repeat the simulations in Table 6 and Table 7 assuming additional non-work related confounding is present alongside an additional single co-exposure asbestos assumed to be moderately correlated (0.1) and strongly correlated (0.5) respectively. Table 15 Table 16 similarly repeat Table 8 and Table 9 for three co-exposures asbestos, diesel, and wood dust. And Table 17 repeats our simulations from Table 10 assuming a more bespoke correlation structure across the four exposures. Again see section 2.7.3 for more details on the bespoke correlation structure proposed.

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with single additional moderately correlated work exposure (asbestos) repeated to include additional non-working confounders.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos corr=0.1** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 11.001 | | | X | X | X |  |  |  |  | x |  |  |
| 11.002 | | | X | X | X | X |  |  |  | x |  |  |
| 11.003 | | | X | X | X |  | X |  |  | x |  |  |
| 11.004 | | | X | X | X |  |  | X |  | x |  |  |
| 11.005 | | | X | X | X |  |  |  | X | x |  |  |
| 11.006 | | | X | X | X | X |  | X |  | x |  |  |
| 11.007 | | | X | X | X | X |  |  | X | x |  |  |
| 11.008 | | | X | X | X |  | X | X |  | x |  |  |
| 11.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 11.101 | | | X | X | X |  |  |  |  | x | x |  |
| 11.102 | | | X | X | X | X |  |  |  | x | x |  |
| 11.103 | | | X | X | X |  | X |  |  | x | x |  |
| 11.104 | | | X | X | X |  |  | X |  | x | x |  |
| 11.105 | | | X | X | X |  |  |  | X | x | x |  |
| 11.106 | | | X | X | X | X |  | X |  | x | x |  |
| 11.107 | | | X | X | X | X |  |  | X | x | x |  |
| 11.108 | | | X | X | X |  | X | X |  | x | x |  |
| 11.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 11.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 11.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 11.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 11.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 11.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 11.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 11.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 11.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 11.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 11.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 11.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 11.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 11.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 11.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 11.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 11.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 11.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 11.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with single additional strongly correlated work exposure (asbestos) repeated to include additional non-working confounders

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos corr=0.5** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 12.001 | | | X | X | X |  |  |  |  | x |  |  |
| 12.002 | | | X | X | X | X |  |  |  | x |  |  |
| 12.003 | | | X | X | X |  | X |  |  | x |  |  |
| 12.004 | | | X | X | X |  |  | X |  | x |  |  |
| 12.005 | | | X | X | X |  |  |  | X | x |  |  |
| 12.006 | | | X | X | X | X |  | X |  | x |  |  |
| 12.007 | | | X | X | X | X |  |  | X | x |  |  |
| 12.008 | | | X | X | X |  | X | X |  | x |  |  |
| 12.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 12.101 | | | X | X | X |  |  |  |  | x | x |  |
| 12.102 | | | X | X | X | X |  |  |  | x | x |  |
| 12.103 | | | X | X | X |  | X |  |  | x | x |  |
| 12.104 | | | X | X | X |  |  | X |  | x | x |  |
| 12.105 | | | X | X | X |  |  |  | X | x | x |  |
| 12.106 | | | X | X | X | X |  | X |  | x | x |  |
| 12.107 | | | X | X | X | X |  |  | X | x | x |  |
| 12.108 | | | X | X | X |  | X | X |  | x | x |  |
| 12.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 12.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 12.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 12.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 12.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 12.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 12.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 12.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 12.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 12.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 12.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 12.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 12.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 12.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 12.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 12.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 12.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 12.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 12.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional moderately correlated work exposures (asbestos, diesel, wood dust) repeated to include additional non-working confounders

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=0.1** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 13.001 | | | X | X | X |  |  |  |  | x |  |  |
| 13.002 | | | X | X | X | X |  |  |  | x |  |  |
| 13.003 | | | X | X | X |  | X |  |  | x |  |  |
| 13.004 | | | X | X | X |  |  | X |  | x |  |  |
| 13.005 | | | X | X | X |  |  |  | X | x |  |  |
| 13.006 | | | X | X | X | X |  | X |  | x |  |  |
| 13.007 | | | X | X | X | X |  |  | X | x |  |  |
| 13.008 | | | X | X | X |  | X | X |  | x |  |  |
| 13.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 13.101 | | | X | X | X |  |  |  |  | x | x |  |
| 13.102 | | | X | X | X | X |  |  |  | x | x |  |
| 13.103 | | | X | X | X |  | X |  |  | x | x |  |
| 13.104 | | | X | X | X |  |  | X |  | x | x |  |
| 13.105 | | | X | X | X |  |  |  | X | x | x |  |
| 13.106 | | | X | X | X | X |  | X |  | x | x |  |
| 13.107 | | | X | X | X | X |  |  | X | x | x |  |
| 13.108 | | | X | X | X |  | X | X |  | x | x |  |
| 13.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 13.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 13.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 13.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 13.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 13.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 13.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 13.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 13.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 13.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 13.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 13.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 13.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 13.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 13.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 13.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 13.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 13.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 13.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional strongly correlated work exposures (asbestos, diesel, wood dust) repeated to include additional non-working confounders

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=0.5** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 14.001 | | | X | X | X |  |  |  |  | x |  |  |
| 14.002 | | | X | X | X | X |  |  |  | x |  |  |
| 14.003 | | | X | X | X |  | X |  |  | x |  |  |
| 14.004 | | | X | X | X |  |  | X |  | x |  |  |
| 14.005 | | | X | X | X |  |  |  | X | x |  |  |
| 14.006 | | | X | X | X | X |  | X |  | x |  |  |
| 14.007 | | | X | X | X | X |  |  | X | x |  |  |
| 14.008 | | | X | X | X |  | X | X |  | x |  |  |
| 14.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 14.101 | | | X | X | X |  |  |  |  | x | x |  |
| 14.102 | | | X | X | X | X |  |  |  | x | x |  |
| 14.103 | | | X | X | X |  | X |  |  | x | x |  |
| 14.104 | | | X | X | X |  |  | X |  | x | x |  |
| 14.105 | | | X | X | X |  |  |  | X | x | x |  |
| 14.106 | | | X | X | X | X |  | X |  | x | x |  |
| 14.107 | | | X | X | X | X |  |  | X | x | x |  |
| 14.108 | | | X | X | X |  | X | X |  | x | x |  |
| 14.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 14.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 14.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 14.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 14.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 14.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 14.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 14.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 14.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 14.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 14.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 14.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 14.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 14.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 14.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 14.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 14.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 14.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 14.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional work exposures (asbestos, diesel, wood dust) with bespoke correlation structure and repeated to include additional non-working confounders

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=bespoke** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 15.001 | | | X | X | X |  |  |  |  | x |  |  |
| 15.002 | | | X | X | X | X |  |  |  | x |  |  |
| 15.003 | | | X | X | X |  | X |  |  | x |  |  |
| 15.004 | | | X | X | X |  |  | X |  | x |  |  |
| 15.005 | | | X | X | X |  |  |  | X | x |  |  |
| 15.006 | | | X | X | X | X |  | X |  | x |  |  |
| 15.007 | | | X | X | X | X |  |  | X | x |  |  |
| 15.008 | | | X | X | X |  | X | X |  | x |  |  |
| 15.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 15.101 | | | X | X | X |  |  |  |  | x | x |  |
| 15.102 | | | X | X | X | X |  |  |  | x | x |  |
| 15.103 | | | X | X | X |  | X |  |  | x | x |  |
| 15.104 | | | X | X | X |  |  | X |  | x | x |  |
| 15.105 | | | X | X | X |  |  |  | X | x | x |  |
| 15.106 | | | X | X | X | X |  | X |  | x | x |  |
| 15.107 | | | X | X | X | X |  |  | X | x | x |  |
| 15.108 | | | X | X | X |  | X | X |  | x | x |  |
| 15.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 15.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 15.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 15.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 15.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 15.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 15.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 15.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 15.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 15.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 15.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 15.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 15.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 15.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 15.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 15.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 15.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 15.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 15.309 | | | X | X | X |  | X |  | X | x | x | x |

### Introducing a single moderating (independent) co-exposure

The co-exposures experienced by an employee during their working life may not only provide an additive increase to their risk, but they may also moderate the risk experienced. Here, the exposure to silica and asbestos for example, may increase the risk experienced at a greater rate than the individual exposures alone.59 This moderating effect can be simulated by including an interaction effect between the two exposures.

Figure – A DAG representing the basic model, multi-independent exposure - outcome relationship with additional confounding and a single moderating co-exposure.

Exposure

Outcome

Co-Exposure(s)

Confounders

Here we simulate a single interaction effect between the two exposures silica and asbestos with a moderating exposure effect of 20%.59 We assume that non-working life confounding is present and initially that only a single independent co-exposure (asbestos) in Table 18 before including additional multiple co-exposures (asbestos, diesel, and wood dust) see Table 19. In both sets of scenarios we only include a single interaction effect between our main exposure silica and our co-exposure asbestos.

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with single additional independent work exposure (asbestos) with additional for non-work confounders where the co-exposure ‘asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Indep Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 16.001 | | | X | X | X |  |  |  |  | x |  |  |
| 16.002 | | | X | X | X | X |  |  |  | x |  |  |
| 16.003 | | | X | X | X |  | X |  |  | x |  |  |
| 16.004 | | | X | X | X |  |  | X |  | x |  |  |
| 16.005 | | | X | X | X |  |  |  | X | x |  |  |
| 16.006 | | | X | X | X | X |  | X |  | x |  |  |
| 16.007 | | | X | X | X | X |  |  | X | x |  |  |
| 16.008 | | | X | X | X |  | X | X |  | x |  |  |
| 16.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 16.101 | | | X | X | X |  |  |  |  | x | x |  |
| 16.102 | | | X | X | X | X |  |  |  | x | x |  |
| 16.103 | | | X | X | X |  | X |  |  | x | x |  |
| 16.104 | | | X | X | X |  |  | X |  | x | x |  |
| 16.105 | | | X | X | X |  |  |  | X | x | x |  |
| 16.106 | | | X | X | X | X |  | X |  | x | x |  |
| 16.107 | | | X | X | X | X |  |  | X | x | x |  |
| 16.108 | | | X | X | X |  | X | X |  | x | x |  |
| 16.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 16.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 16.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 16.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 16.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 16.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 16.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 16.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 16.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 16.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 16.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 16.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 16.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 16.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 16.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 16.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 16.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 16.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 16.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) with multiple additional independent work exposure (asbestos, diesel, wood dust) with additional for non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Multi-Indep Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 17.001 | | | X | X | X |  |  |  |  | x |  |  |
| 17.002 | | | X | X | X | X |  |  |  | x |  |  |
| 17.003 | | | X | X | X |  | X |  |  | x |  |  |
| 17.004 | | | X | X | X |  |  | X |  | x |  |  |
| 17.005 | | | X | X | X |  |  |  | X | x |  |  |
| 17.006 | | | X | X | X | X |  | X |  | x |  |  |
| 17.007 | | | X | X | X | X |  |  | X | x |  |  |
| 17.008 | | | X | X | X |  | X | X |  | x |  |  |
| 17.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 17.101 | | | X | X | X |  |  |  |  | x | x |  |
| 17.102 | | | X | X | X | X |  |  |  | x | x |  |
| 17.103 | | | X | X | X |  | X |  |  | x | x |  |
| 17.104 | | | X | X | X |  |  | X |  | x | x |  |
| 17.105 | | | X | X | X |  |  |  | X | x | x |  |
| 17.106 | | | X | X | X | X |  | X |  | x | x |  |
| 17.107 | | | X | X | X | X |  |  | X | x | x |  |
| 17.108 | | | X | X | X |  | X | X |  | x | x |  |
| 17.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 17.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 17.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 17.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 17.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 17.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 17.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 17.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 17.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 17.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 17.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 17.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 17.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 17.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 17.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 17.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 17.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 17.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 17.309 | | | X | X | X |  | X |  | X | x | x | x |

### Introducing a single moderating (correlated) co-exposure

We then extend the scenario to assume that the co-exposures are correlated to varying strengths.

Figure – A DAG representing the, multi- correlated exposure(s) - outcome relationship with additional confounding and a single moderating co-exposure.

Exposure

Outcome

Co-Exposure(s)

Confounders

Table 20 and Table 21 repeat the single co-exposure model with increasing correlation strength between the main exposure and the co-exposures (corr = 0.1 and 0.5 respectively) and containing an additional moderating effect of 20%.

Table 22 Table 23 repeat the multiple co-exposure model with increasing correlation strength between the main exposure and the multiple co-exposures (corr = 0.1 and 0.5 respectively) and containing an additional moderating effect of 20% for the single co-exposure ‘asbestos’. Table 24 repeats assuming a bespoke underling correlation structure between the multiple co-exposures.

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) a single additional moderately correlated work exposure (asbestos) with additional for non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **20%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos corr=0.1** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 18.001 | | | X | X | X |  |  |  |  | x |  |  |
| 18.002 | | | X | X | X | X |  |  |  | x |  |  |
| 18.003 | | | X | X | X |  | X |  |  | x |  |  |
| 18.004 | | | X | X | X |  |  | X |  | x |  |  |
| 18.005 | | | X | X | X |  |  |  | X | x |  |  |
| 18.006 | | | X | X | X | X |  | X |  | x |  |  |
| 18.007 | | | X | X | X | X |  |  | X | x |  |  |
| 18.008 | | | X | X | X |  | X | X |  | x |  |  |
| 18.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 18.101 | | | X | X | X |  |  |  |  | x | x |  |
| 18.102 | | | X | X | X | X |  |  |  | x | x |  |
| 18.103 | | | X | X | X |  | X |  |  | x | x |  |
| 18.104 | | | X | X | X |  |  | X |  | x | x |  |
| 18.105 | | | X | X | X |  |  |  | X | x | x |  |
| 18.106 | | | X | X | X | X |  | X |  | x | x |  |
| 18.107 | | | X | X | X | X |  |  | X | x | x |  |
| 18.108 | | | X | X | X |  | X | X |  | x | x |  |
| 18.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 18.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 18.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 18.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 18.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 18.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 18.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 18.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 18.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 18.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 18.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 18.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 18.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 18.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 18.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 18.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 18.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 18.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 18.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) a single additional strongly correlated work exposure (asbestos) with additional for non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **50%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos corr=0.5** | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 19.001 | | | X | X | X |  |  |  |  | x |  |  |
| 19.002 | | | X | X | X | X |  |  |  | x |  |  |
| 19.003 | | | X | X | X |  | X |  |  | x |  |  |
| 19.004 | | | X | X | X |  |  | X |  | x |  |  |
| 19.005 | | | X | X | X |  |  |  | X | x |  |  |
| 19.006 | | | X | X | X | X |  | X |  | x |  |  |
| 19.007 | | | X | X | X | X |  |  | X | x |  |  |
| 19.008 | | | X | X | X |  | X | X |  | x |  |  |
| 19.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 19.101 | | | X | X | X |  |  |  |  | x | x |  |
| 19.102 | | | X | X | X | X |  |  |  | x | x |  |
| 19.103 | | | X | X | X |  | X |  |  | x | x |  |
| 19.104 | | | X | X | X |  |  | X |  | x | x |  |
| 19.105 | | | X | X | X |  |  |  | X | x | x |  |
| 19.106 | | | X | X | X | X |  | X |  | x | x |  |
| 19.107 | | | X | X | X | X |  |  | X | x | x |  |
| 19.108 | | | X | X | X |  | X | X |  | x | x |  |
| 19.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 19.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 19.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 19.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 19.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 19.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 19.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 19.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 19.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 19.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 19.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 19.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 19.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 19.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 19.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 19.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 19.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 19.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 19.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) a multiple additional moderately correlated work exposure (asbestos, diesel, Wood dust) with additional non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=0.1** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **50%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 20.001 | | | X | X | X |  |  |  |  | x |  |  |
| 20.002 | | | X | X | X | X |  |  |  | x |  |  |
| 20.003 | | | X | X | X |  | X |  |  | x |  |  |
| 20.004 | | | X | X | X |  |  | X |  | x |  |  |
| 20.005 | | | X | X | X |  |  |  | X | x |  |  |
| 20.006 | | | X | X | X | X |  | X |  | x |  |  |
| 20.007 | | | X | X | X | X |  |  | X | x |  |  |
| 20.008 | | | X | X | X |  | X | X |  | x |  |  |
| 20.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 20.101 | | | X | X | X |  |  |  |  | x | x |  |
| 20.102 | | | X | X | X | X |  |  |  | x | x |  |
| 20.103 | | | X | X | X |  | X |  |  | x | x |  |
| 20.104 | | | X | X | X |  |  | X |  | x | x |  |
| 20.105 | | | X | X | X |  |  |  | X | x | x |  |
| 20.106 | | | X | X | X | X |  | X |  | x | x |  |
| 20.107 | | | X | X | X | X |  |  | X | x | x |  |
| 20.108 | | | X | X | X |  | X | X |  | x | x |  |
| 20.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 20.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 20.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 20.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 20.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 20.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 20.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 20.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 20.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 20.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 20.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 20.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 20.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 20.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 20.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 20.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 20.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 20.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 20.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) multiple additional strongly correlated work exposure (asbestos, diesel, Wood dust) with additional non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=0.5** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **50%** | **5yr** | **10yr** | **5yr** | **10yr** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 21.001 | | | X | X | X |  |  |  |  | x |  |  |
| 21.002 | | | X | X | X | X |  |  |  | x |  |  |
| 21.003 | | | X | X | X |  | X |  |  | x |  |  |
| 21.004 | | | X | X | X |  |  | X |  | x |  |  |
| 21.005 | | | X | X | X |  |  |  | X | x |  |  |
| 21.006 | | | X | X | X | X |  | X |  | x |  |  |
| 21.007 | | | X | X | X | X |  |  | X | x |  |  |
| 21.008 | | | X | X | X |  | X | X |  | x |  |  |
| 21.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 21.101 | | | X | X | X |  |  |  |  | x | x |  |
| 21.102 | | | X | X | X | X |  |  |  | x | x |  |
| 21.103 | | | X | X | X |  | X |  |  | x | x |  |
| 21.104 | | | X | X | X |  |  | X |  | x | x |  |
| 21.105 | | | X | X | X |  |  |  | X | x | x |  |
| 21.106 | | | X | X | X | X |  | X |  | x | x |  |
| 21.107 | | | X | X | X | X |  |  | X | x | x |  |
| 21.108 | | | X | X | X |  | X | X |  | x | x |  |
| 21.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 21.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 21.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 21.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 21.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 21.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 21.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 21.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 21.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 21.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 21.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 21.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 21.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 21.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 21.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 21.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 21.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 21.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 21.309 | | | X | X | X |  | X |  | X | x | x | x |

Table - Scenarios to be simulated for Single Exposure (Random Work Duration) multiple additional ‘bespoke’ correlated work exposure (asbestos, diesel, wood dust) with additional non-work confounders where the co-exposure ‘Asbestos’ is assumed to moderate the main ‘silica’ effect by 20%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Cohort Sample Size (Scenario No)** | | | **Effect Size ‘known truth’** | | | **Latency Period** | | **Risk Decay Half Life** | | **Correlated Working Life Co-exposures corr=bespoke** | **Co-exp Decay Half-life** | **Co-exp Latency Period** |
|  | **1000** | **10000** | **100000** | **2%** | **5%** | **50%** | **5yr** | **10yrs** | **5yr** | **10yrs** | **Asbestos|Diesel|** wood dust | **5** | **5** |
| **Randomly allocated exposure period (mean 30yrs, s.d. 5yrs)** | 22.001 | | | X | X | X |  |  |  |  | x |  |  |
| 22.002 | | | X | X | X | X |  |  |  | x |  |  |
| 22.003 | | | X | X | X |  | X |  |  | x |  |  |
| 22.004 | | | X | X | X |  |  | X |  | x |  |  |
| 22.005 | | | X | X | X |  |  |  | X | x |  |  |
| 22.006 | | | X | X | X | X |  | X |  | x |  |  |
| 22.007 | | | X | X | X | X |  |  | X | x |  |  |
| 22.008 | | | X | X | X |  | X | X |  | x |  |  |
| 22.009 | | | X | X | X |  | X |  | X | x |  |  |
|  | 22.101 | | | X | X | X |  |  |  |  | x | x |  |
| 22.102 | | | X | X | X | X |  |  |  | x | x |  |
| 22.103 | | | X | X | X |  | X |  |  | x | x |  |
| 22.104 | | | X | X | X |  |  | X |  | x | x |  |
| 22.105 | | | X | X | X |  |  |  | X | x | x |  |
| 22.106 | | | X | X | X | X |  | X |  | x | x |  |
| 22.107 | | | X | X | X | X |  |  | X | x | x |  |
| 22.108 | | | X | X | X |  | X | X |  | x | x |  |
| 22.109 | | | X | X | X |  | X |  | X | x | x |  |
|  | 22.201 | | | X | X | X |  |  |  |  | x |  | x |
|  | 22.202 | | | X | X | X | X |  |  |  | x |  | x |
|  | 22.203 | | | X | X | X |  | X |  |  | x |  | x |
|  | 22.204 | | | X | X | X |  |  | X |  | x |  | x |
|  | 22.205 | | | X | X | X |  |  |  | X | x |  | x |
|  | 22.206 | | | X | X | X | X |  | X |  | x |  | x |
|  | 22.207 | | | X | X | X | X |  |  | X | x |  | x |
|  | 22.208 | | | X | X | X |  | X | X |  | x |  | x |
|  | 22.209 | | | X | X | X |  | X |  | X | x |  | x |
|  | 22.301 | | | X | X | X |  |  |  |  | x | x | x |
|  | 22.302 | | | X | X | X | X |  |  |  | x | x | x |
|  | 22.303 | | | X | X | X |  | X |  |  | x | x | x |
|  | 22.304 | | | X | X | X |  |  | X |  | x | x | x |
|  | 22.305 | | | X | X | X |  |  |  | X | x | x | x |
|  | 22.306 | | | X | X | X | X |  | X |  | x | x | x |
|  | 22.307 | | | X | X | X | X |  |  | X | x | x | x |
|  | 22.308 | | | X | X | X |  | X | X |  | x | x | x |
|  | 22.309 | | | X | X | X |  | X |  | X | x | x | x |

# Analysis methods

## Defining the data generation (Random number generation)

To ensure the results of the simulation study performed here are 1) repeatable and 2) any errors can be checked, the series of random numbers used to generate each dataset are produced from a pseudo random number generator. Simulations are considered fully independent if using different starting seeds to generate datasets for each scenario.60 Each scenario therefore requires its own seed, with the difference between each seed greater than the sample size for the scenario. To accomplish this the seed shall be predefined as the scenario number identified in Section 0 plus the date of the first EPHOR project kick-off meeting began i.e. 28/01/2020. For example, scenario 1.001 the seed will be set to 100128012020, scenario 1.010 will be 101028012020, scenario 2.109 becomes 210928012020, and so on.

## Estimating the Health Impact of the Intervention

#### To compare how varying exposome characteristics influence the effect of our proposed interventions, we need to quantify the health impact before and after the intervention has been applied. In order to keep the simulation procedure simple and efficient, we propose to compare the Average Time to event (often called Average Life Expectancy when even is mortality), Expected No. of people reaching 65 without diagnosis.

#### Average time to event Expectancy

#### The average life expectancy will be calculated from the survival curve based on restricted/extended mean survival. The restricted mean is calculated as the area under the Kaplan–Meier product-limit survivor curve. The extended mean is obtained by extending the survivor curve to zero using an exponentially fitted curve.61 We will calculate the mean difference for a simulated cohort with raw RCS exposure (i.e. no-intervention), and repeated for each proposed exposure intervention. The Associated 95% confidence intervals will be calculated using he standard error reported in the repeated simulations.

#### Expected increase in people reaching a given age (e.g. 65 years).

#### The number of people (per 100,000) reaching 65 will be calculated and the difference between raw exposure and reduced exposure will be compared across exposome characteristics.

* ***Alternatives? Maybe Lifetables analysis? PAF? Disability Adjusted Life Years? – These may require too much computational time to do for 1000 simulations of sample sizes up to 100000?***

## Summarising results, and assessing performance of Health Interventions, comparing within and between scenarios

Within each scenario, we can compare the three estimates of health impact (e.g. average time to event) for each intervention and the non-intervention state. For each scenario, health intervention, and cohort size there will be three estimates of the health impact associated with the size of the main exposure ‘RCS’ effect (see Section 2.7.1). Here these health impact estimates will be compared to the non-intervention state i.e. what would happen if no intervention occurred. The difference in health impact observed for each intervention state compared to the non-intervention state will be stored for each *ith* simulated dataset for each scenario. This will enable any further review of factors not observed in the summary measure alone, or to retrospectively calculate any summary measures thought useful post generation. In addition, we will store the within simulation outcome measure, and corresponding standard error if present for each intervention state.

### Summarising each intervention effect across the simulations

As is standard in simulations studies62 we will summarise the estimates of the simulated data by reporting the average estimate of interest i.e. the mean outcome for each intervention state including the non-intervention state. The average of the within simulation standard error ave. will both be produced in order to determine if bias is present in the estimates.

#### Average estimate (i.e. the mean of each intervention effect)

Here the B is the number of simulations performed.

#### Average of the within simulation standard error (Monte Carlo SE)

### Assessing the performance of each intervention effect

To evaluate performance of the intervention within each scenario we will compare to the non-intervention. We will produce a simple paired sample mean differences, paired sample standard errors, the 95% Confidence intervals, and corresponding p-value from a pair sample t-test.

#### Average estimate (i.e. the mean difference of each intervention effect compared to no intervention)

Here, is the difference in health effect between intervention and no intervention where s the health effect observed for the jth intervention on the ith simulation, and is the health effect observed when no intervention was present.

#### Empirical standard error

We will then report the corresponding result of the paired samples t-test and 95% Confidence intervals associated with the mean difference.

## Defining the Sample size & Simulation No.

We will be sampling from an infinite population with known true parameters. Data is generated by producing random draws from a known parametric model, in this case the Gompertz parametric distribution (see section 2.4). Through repeated simulations we can assess the performance of the intervention compared to no intervention under varying characteristics of the exposome that are manipulated within each scenario. The following outlines our definition of the within cohort sample size and the number of repeated simulations to provide a reliable result not related to random chance alone.

#### Sample Size of Simulated Datasets

The sample size of each simulated datasets is one characteristic that is to be manipulated. Here the sample sizes within each simulated dataset are defined to be representative of empirical real world studies that have been or could be performed in occupational health. Typically these studies might be at the local, national or international level for a particular occupational group. We therefore defined the sample sizes to represent studies of size small (n=1000), medium (10,000), and large (100,000) subjects.

#### Sample Size of No. of simulated datasets

In most simulation studies the sample size calculation for the number of simulations being performed is based on the key performance measure being the bias associated with an estimation of the main exposure effect.63 Here we are interested in being able to determine if a health intervention is providing a significant improvement in health of the population, where our primary measure of health is ‘average time to event’ in this case years to diagnosis. If we assume a paired sample t-test design, a minimum clinically important improvement would be 1 year i.e. the difference in intervention vs not sees average time to diagnosis increase by 1 year, and the standard error associated with a difference is 10 years. Then to see a significant differences at the 5% level with corresponding power of 80%, then we would need 787 simulations per scenario. At 90% power it would need 1053 simulations. Given the limited impact to time and costs of increasing the number of simulations, we will perform 1000 simulations per scenario. We will reassess this once the initial simulations are performed.

# Results

# Discussion/Conclusion

## Conclusion

# References

1. Humans IWGotEoCRt. Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum* 2012;100(Pt C):11-465. [published Online First: 2012/11/30]

2. Checkoway H, Heyer NJ, Seixas NS, et al. Dose-response associations of silica with nonmalignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. *American Journal of Epidemiology* 1997;145(8):680-88. doi: 10.1093/aje/145.8.680

3. Rice FL, Park R, Stayner L, et al. Crystalline silica exposure and lung cancer mortality in diatomaceous earth industry workers: a quantitative risk assessment. *Occupational and Environmental Medicine* 2001;58(1):38-45. doi: 10.1136/oem.58.1.38

4. Steenland K, Brown D. MORTALITY STUDY OF GOLD MINERS EXPOSED TO SILICA AND NONASBESTIFORM AMPHIBOLE MINERALS - AN UPDATE WITH 14 MORE YEARS OF FOLLOW-UP. *American Journal of Industrial Medicine* 1995;27(2):217-29. doi: 10.1002/ajim.4700270207

5. Hnizdo E, Sluiscremer GK. SILICA EXPOSURE, SILICOSIS, AND LUNG-CANCER - A MORTALITY STUDY OF SOUTH-AFRICAN GOLD MINERS. *British Journal of Industrial Medicine* 1991;48(1):53-60.

6. Carta P, Aru G, Manca P. Mortality from lung cancer among silicotic patients in Sardinia: an update study with 10 more years of follow up. *Occupational and Environmental Medicine* 2001;58(12):786-93. doi: 10.1136/oem.58.12.786

7. Attfield MD, Costello J. Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers. *American Journal of Industrial Medicine* 2004;45(2):129-38. doi: 10.1002/ajim.10348

8. Steenland K, Sanderson W. Lung cancer among industrial sand workers exposed to crystalline silica. *American Journal of Epidemiology* 2001;153(7):695-703. doi: 10.1093/aje/153.7.695

9. Brown TP, Rushton L. Mortality in the UK industrial silica sand industry: 1. Assessment of exposure to respirable crystalline silica. *Occupational and Environmental Medicine* 2005;62(7):442-45. doi: 10.1136/oem.2004.017715

10. Brown TP, Rushton L. Mortality in the UK industrial silica sand industry: 2. A retrospective cohort study. *Occupational and Environmental Medicine* 2005;62(7):446-52. doi: 10.1136/oem.2004.017731

11. Reid PJ, SluisCremer GK. Mortality of white South African gold miners. *Occupational and Environmental Medicine* 1996;53(1):11-16. doi: 10.1136/oem.53.1.11

12. Hnizdo E, Murray J, Klempman S. Lung cancer in relation to exposure to silica dust, silicosis and uranium production in South African gold miners. *Thorax* 1997;52(3):271-75. doi: 10.1136/thx.52.3.271

13. Cherry NM, Burgess GL, Turner S, et al. Crystalline silica and risk of lung cancer in the potteries. *Occupational and Environmental Medicine* 1998;55(11):779-85. doi: 10.1136/oem.55.11.779

14. McDonald JC, McDonald AD, Hughes JM, et al. Mortality from lung and kidney disease in a cohort of North American industrial sand workers: An update. *Annals of Occupational Hygiene* 2005;49(5):367-73. doi: 10.1093/annhyg/mei001

15. Xu ZY, Brown LM, Pan GW, et al. Cancer risks among iron and steel workers in Anshan, China .2. Case-control studies of lung and stomach cancer. *American Journal of Industrial Medicine* 1996;30(1):7-15.

16. Westberg HB, Bellander T. Epidemiological adaptation of quartz exposure modeling in Swedish aluminum foundries: nested case-control study on lung cancer. *Appl Occup Environ Hyg* 2003;18(12):1006-13. doi: 10.1080/10473220390244676 [published Online First: 2003/11/13]

17. Steenland K, Mannetje A, Boffetta P, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes & Control* 2001;12(9):773-84. doi: 10.1023/a:1012214102061

18. Shahbazi F, Morsali M, Poorolajal J. The effect of silica exposure on the risk of lung cancer: A dose-response meta-analysis. *Cancer Epidemiology* 2021;75 doi: 10.1016/j.canep.2021.102024

19. CRUK. Cancer Research UK: Lung Cancer Risk 2019 [updated 11 September 2018; cited 2021 Oct 2021]. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/risk-factors#heading-Zero> accessed Oct 2021 2021.

20. Bender R, Augustin T, Blettner M. Generating survival times to simulate Cox proportional hazards models. *Statistics in Medicine* 2005;24(11):1713-23. doi: 10.1002/sim.2059

21. Crowther MJ. Simulating time-to-event data from parametric distributions, custom distributions, competings risk models and general multi-state models. *arXiv preprint arXiv:211010414* 2021

22. Leemis LM, Shih LH, Reynertson K. VARIATE GENERATION FOR ACCELERATED LIFE AND PROPORTIONAL HAZARDS MODELS WITH TIME-DEPENDENT COVARIATES. *Statistics & Probability Letters* 1990;10(4):335-39. doi: 10.1016/0167-7152(90)90052-9

23. Lee ET, Go OT. Survival analysis in public health research. *Annual Review of Public Health* 1997;18:105-34. doi: 10.1146/annurev.publhealth.18.1.105

24. Creely KS, Cowie H, Van Tongeren M, et al. Trends in inhalation exposure - A review of the data in the published scientific literature. *Annals of Occupational Hygiene* 2007;51(8):665-78. doi: 10.1093/annhyg/mem050

25. Austin PC. Generating survival times to simulate Cox proportional hazards models with time-varying covariates. *Statistics in Medicine* 2012;31(29):3946-58. doi: 10.1002/sim.5452

26. Breslow NE, Day NE. Statistical methods in cancer research : vol.II: The design and analysis of cohort studies: hap. 6: Modelling the relationship between risk, dose and time.1987.

27. Thomas DC, Thomas DC, ProQuest. Statistical methods in environmental epidemiology. Proceedings of a symposium on time-related factors in cancer epidemiology.2009.

28. Armstrong B. Models for the relationship between ambient temperature and daily mortality. *Epidemiology* 2006;17(6):624-31. doi: 10.1097/01.ede.0000239732.50999.8f [published Online First: 2006/10/10]

29. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. *Stat Med* 2014;33(5):881-99. doi: 10.1002/sim.5963 [published Online First: 2013/09/13]

30. Sylvestre MP, Abrahamowicz M. Comparison of algorithms to generate event times conditional on time-dependent covariates. *Stat Med* 2008;27(14):2618-34. doi: 10.1002/sim.3092 [published Online First: 2007/10/09]

31. Mackenzie T, Abrahamowicz M. Marginal and hazard ratio specific random data generation: Applications to semi-parametric bootstrapping. *Statistics and Computing* 2002;12(3):245-52. doi: 10.1023/a:1020750810409

32. EU. Employment, Social Affairs & Inclusion: Guidance for National Labour Inspectors on addressing risks from worker exposure to respirable crystalline silica (RCS) on construction sites 2016 [Available from: <https://osha.europa.eu/en/node/10407>.

33. van Deurssen E, Pronk A, Spaan S, et al. Quartz and Respirable Dust in the Dutch Construction Industry: A Baseline Exposure Assessment as Part of a Multidimensional Intervention Approach. *Annals of Occupational Hygiene* 2014;58(6):724-38. doi: 10.1093/annhyg/meu021

34. Sauve JF, Beaudry C, Begin D, et al. Statistical modeling of crystalline silica exposure by trade in the construction industry using a database compiled from the literature. *Journal of Environmental Monitoring* 2012;14(9):2512-20. doi: 10.1039/c2em30443k

35. Boudigaard SH, Hansen KK, Kolstad H, et al. Determinants of Respirable Quartz Exposure Concentrations Across Occupations in Denmark, 2018. *Ann Work Expo Health* 2021 doi: 10.1093/annweh/wxab116 [published Online First: 2021/12/22]

36. Nij ET, Hohr D, Borm P, et al. Variability in quartz exposure in the construction industry: Implications for assessing exposure-response relations. *Journal of Occupational and Environmental Hygiene* 2004;1(3):191-98. doi: 10.1080/15459620490424528

37. Rappaport SM. ASSESSMENT OF LONG-TERM EXPOSURES TO TOXIC-SUBSTANCES IN AIR. *Annals of Occupational Hygiene* 1991;35(1):61-121. doi: 10.1093/annhyg/35.1.61

38. eurostat. Employed persons, average number of years spent working, by sex and economic activity: Table LFSO\_06YRSPNA11. European commission. 2014 [updated 08/02/2021. Available from: <https://ec.europa.eu/eurostat/databrowser/view/LFSO_06YRSPNA11__custom_2005443/default/bar?lang=en>. accessed 31/01/2022.

39. HSE. The Health and Safety Executive: Asbestos health and safety 2020 [Available from: <https://www.hse.gov.uk/asbestos/index.htm> accessed Dec 2021 2021.

40. Fonseca AS, Jorgensen AK, Larsen BX, et al. Historical Asbestos Measurements in Denmark-A National Database. *Int J Environ Res Public Health* 2022;19(2) doi: 10.3390/ijerph19020643 [published Online First: 2022/01/22]

41. Scarselli A, Corfiati M, Di Marzio D. Occupational exposure in the removal and disposal of asbestos-containing materials in Italy. *International Archives of Occupational and Environmental Health* 2016;89(5):857-65. doi: 10.1007/s00420-016-1126-6

42. Lenters V, Vermeulen R, Dogger S, et al. A Meta-analysis of Asbestos and Lung Cancer: Is Better Quality Exposure Assessment Associated with Steeper Slopes of the Exposure-Response Relationships? *Environmental Health Perspectives* 2011;119(11):1547-55. doi: 10.1289/ehp.1002879

43. Lewne M, Plato N, Gustavsson P. Exposure to particles, elemental carbon and nitrogen dioxide in workers exposed to motor exhaust. *Annals of Occupational Hygiene* 2007;51(8):693-701. doi: 10.1093/annhyg/mem046

44. Galea KS, Mair C, Alexander C, et al. Occupational Exposure to Respirable Dust, Respirable Crystalline Silica and Diesel Engine Exhaust Emissions in the London Tunnelling Environment. *Annals of Occupational Hygiene* 2016;60(2):263-69. doi: 10.1093/annhyg/mev067

45. Ziembicki S, Kirkham TL, Demers PA, et al. Diesel Engine Exhaust Exposure in the Ontario Civil Infrastructure Construction Industry. *Ann Work Expo Health* 2022;66(2):150-62. doi: 10.1093/annweh/wxab068 [published Online First: 2021/09/30]

46. Vermeulen R, Silverman DT, Garshick E, et al. Exposure-Response Estimates for Diesel Engine Exhaust and Lung Cancer Mortality Based on Data from Three Occupational Cohorts. *Environmental Health Perspectives* 2014;122(2):172-77. doi: 10.1289/ehp.1306880

47. Spee T, Van De Rijdt-Van Hoof E, Van Hoof W, et al. Exposure to wood dust among carpenters in the construction industry in The Netherlands. *Annals of Occupational Hygiene* 2007;51(3):241-48. doi: 10.1093/annhyg/mel075

48. Black N, Dilworth M, Summers N. Occupational exposure to wood dust in the British woodworking industry in 1999/2000. *Annals of Occupational Hygiene* 2007;51(3):249-60. doi: 10.1093/annhyg/mem007

49. Hancock DG, Langley ME, Chia KL, et al. Wood dust exposure and lung cancer risk: a meta-analysis. *Occupational and Environmental Medicine* 2015;72(12):889-U89. doi: 10.1136/oemed-2014-102722

50. Vallieres E, Pintos J, Parent ME, et al. Occupational exposure to wood dust and risk of lung cancer in two population-based case-control studies in Montreal, Canada. *Environmental Health* 2015;14 doi: 10.1186/1476-069x-14-1

51. ONS. ONS: Employment by industry 2021 [updated 16 November 2021. Available from: <https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/datasets/employmentbyindustryemp13> accessed 12th Dec 2021 2021.

52. CRUK. Cancer Research UK: Lung cancer incidence statistics 2016-2018 2019 [updated 4th Oct 2021. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-One> accessed 10th Dec 2021.

53. Bray FI, Weiderpass E. Lung cancer mortality trends in 36 European countries: secular trends and birth cohort patterns by sex and region 1970-2007. *Int J Cancer* 2010;126(6):1454-66. doi: 10.1002/ijc.24855 [published Online First: 2009/09/04]

54. Murphy CC, Yang YC. Use of age-period-cohort analysis in cancer epidemiology research. *Curr Epidemiol Rep* 2018;5(4):418-31. doi: 10.1007/s40471-018-0174-8 [published Online First: 2019/04/24]

55. HSE. The Health and Saftey Executive: Occupational Cancer statistics in Great Britain, 2020 [updated Dec 2019. Available from: <https://www.hse.gov.uk/sTATIsTICs/causdis/cancer.pdf> accessed 10th September 2021 2021.

56. Ohlander J, Kromhout H, van Tongeren M. Interventions to Reduce Exposures in the Workplace: A Systematic Review of Intervention Studies Over Six Decades, 1960-2019. *Front Public Health* 2020;8:67. doi: 10.3389/fpubh.2020.00067 [published Online First: 2020/03/27]

57. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10(1):37-48. doi: 10.1097/00001648-199901000-00008

58. Williams TC, Bach CC, Matthiesen NB, et al. Directed acyclic graphs: a tool for causal studies in paediatrics. *Pediatric Research* 2018;84(4):487-93. doi: 10.1038/s41390-018-0071-3

59. Lacourt A, Gramond C, Audignon S, et al. Pleural mesothelioma and occupational coexposure to asbestos, mineral wool, and silica. *Am J Respir Crit Care Med* 2013;187(9):977-82. doi: 10.1164/rccm.201210-1911OC [published Online First: 2013/03/09]

60. Burton A, Altman DG, Royston P, et al. The design of simulation studies in medical statistics. *Stat Med* 2006;25(24):4279-92. doi: 10.1002/sim.2673 [published Online First: 2006/09/02]

61. Klein JP, Moeschberger ML, collection EBe. Survival Analysis : Techniques for Censored and Truncated Data2003.

62. Demirtas H. The design of simulation studies in medical statistics. *Statistics in Medicine* 2007;26(20):3818-21. doi: 10.1002/sim.2876

63. Morris TP, White IR, Crowther MJ. Using simulation studies to evaluate statistical methods. *Statistics in Medicine* 2019;38(11):2074-102. doi: 10.1002/sim.8086