Probability of Causation: ECHA Systematic Review with Meta-regression

Lung cancer due to occupational asbestos exposure

Javier Mancilla-Galindo Susan Peters Jenny Deng
Henk van der Molen Hans Kromhout Lützen Portengen
Roel Vermeulen Dick Heederik

2025-08-13

Table of contents

Spline Model

This model incorporates the the exposure-response relation from nonlinear meta-regression models as determined by Lenters, et al.[1] and van der Bij, et al.[2], and updated in the scientific opinion for the European Chemicals Agency (ECHA).[3] The underlying data and results of the meta-regression are contained within the list element `MOD`. Tailored-made functions are sourced into this analysis, namely:

- `predict.nsplin`: Generates predictions using natural spline transformations based on the provided model object.
- `getRR`: Calculate relative risk (RR) based on a specified (linear/spline) model that estimates the exposure-response relationship.
- `getPoC`: Calculate probability of causation (PoC) based on the RR obtained from getRR function.

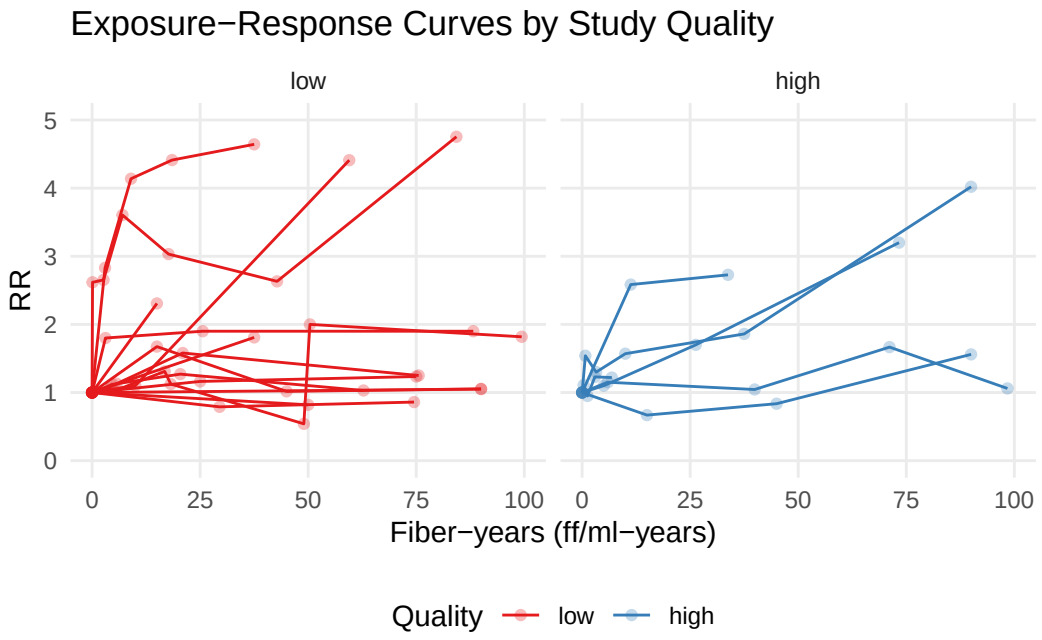
```
MOD <- readRDS(file.path(inputfolder,"MOD.rds"))
source("scripts/predict.nsplin.R")
source("scripts/getRR.R")
source("scripts/getPoC.R")
```

There are 4 different models possible:

1. linear model, assumes difference in background rate of outcome
2. linear model, assumes no difference in background rate of outcome
3. spline model, assumes difference in background rate of outcome
4. spline model, assumes no difference in background rate of outcome

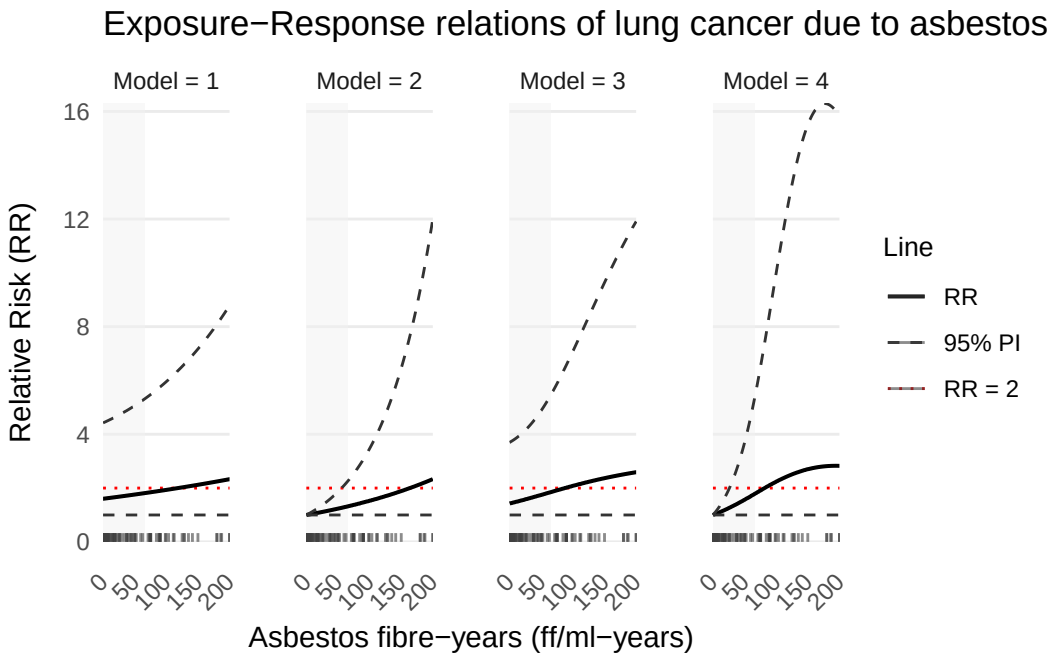
The range of reported exposure values greater than 0 for the pooled estimates in ECHA is 0.1 - 4710 fiber-years, with a median of 89.1 (IQR: 19.9 - 252.4)

The I-square statistic for model 4 (spline, no difference in background rate) is **92.7%**. The following plot shows the relative risk estimates reported by study, grouped by quality of exposure assessment. The plot data margins were fixed to y = 5 and x = 100 to focus on lower exposure values, thus resulting in the removal of 52 rows out of 134.



Exposure-response

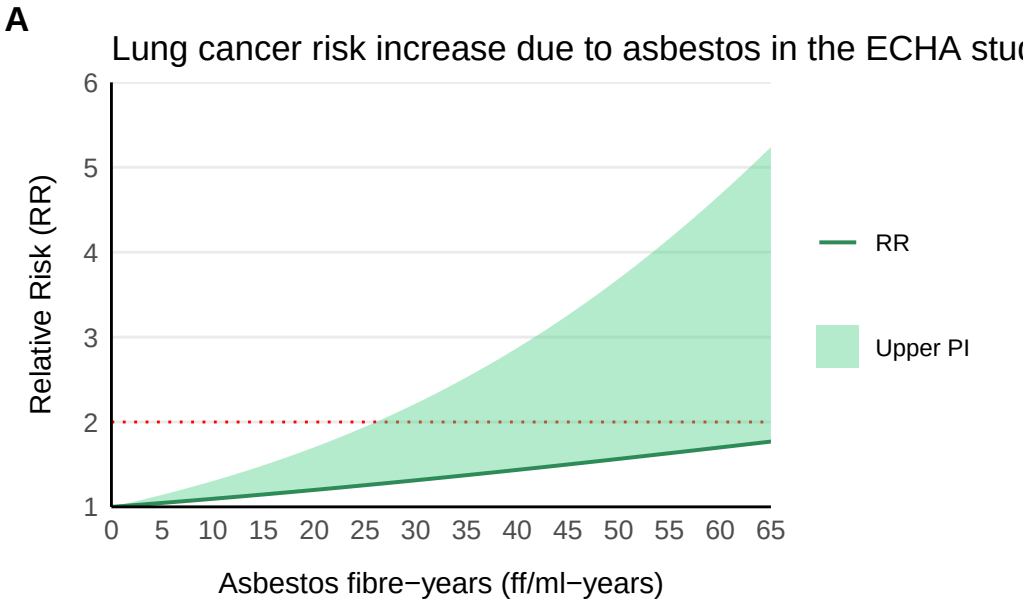
Shape of the exposure response under the 0-200 fiber-years range:



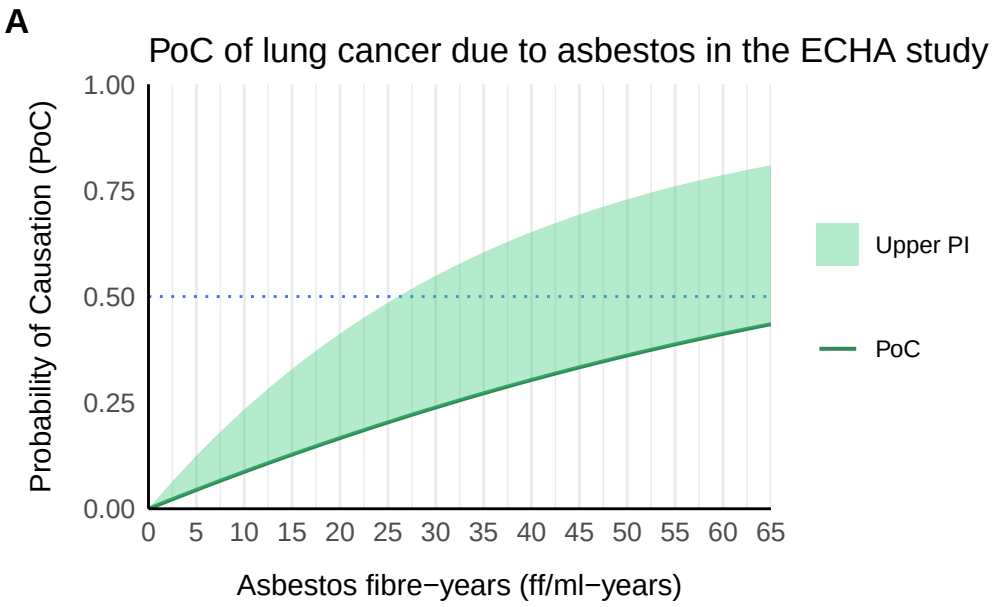
This figure shows that a doubling in the risk of lung cancer (RR = 2) is not expected to be seen with the values of exposure observed in the SYNERGY study (shaded area).

Using modelling strategy number 4, and the actual exposure data in SYNERGY, the PoC and prediction intervals as a measure of uncertainty from study heterogeneity can be obtained following Higgins, et al. method.[4]

This is the plot of lung cancer risk ratio with the observed exposure values in this study:



And the probability of causation, with the upper prediction interval:



Asbestos Exposure-Response in ECHA (Spline Model)

Model	Risk Increase per Fibre-year[1,2]		Min Exposure for 50% PoC (fibre-years)[3]		Cases per 10,000 above 50% PoC in SYNERGY	
	Estimate	95% Prediction Interval	Point Estimate	Presumably Plausible	Point Estimate	Presumably Plausible
Spline	0.9%	0% ; 2.6%	81.71	26.09	0	3

[1]Not applicable for non-linear spline model
[2]Instantaneous slope at 1.5 fibre-years (median exposure in SYNERGY cases)
[3]Probability of Causation (PoC)

Participants with outcome and a PoC greater than or equal to 50%:

References

1 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: 1547–1555.

2 Van Der Bij S, Koffijberg H, Lenters V, *et al.* Lung cancer risk at low cumulative asbestos exposure: Meta-regression of the exposure–response relationship. *Cancer Causes & Control* 2013; 24: 1–12.

3 Heederik D, Santonen T. Opinion on scientific evaluation of occupational exposure limits for Asbestos [Internet]. European Chemicals Agency; 2021 Jun p. 16Report No.: ECHA/RAC/A77-O-0000006981-66-01/F. Available from: https://echa.europa.eu/documents/10162/7937606/OEL_asbestos_Final_Opinion_en.pdf/.

4 Higgins JPT, Thompson SG, Spiegelhalter DJ. A Re-Evaluation of Random-Effects Meta-Analysis. *Journal of the Royal Statistical Society Series A: Statistics in Society* 2009; 172: 137–159.

Package References

For specific information on the operating system, R version, and R package versions used, please refer to the **R/session** folder in the GitHub repository.

- Auguie B (2017). *gridExtra: Miscellaneous Functions for "Grid" Graphics*. doi:10.32614/CRAN.package.gridExtra https://doi.org/10.32614/CRAN.package.gridExtra, R package version 2.3, https://CRAN.R-project.org/package=gridExtra.
- Bates D, Maechler M, Jagan M (2025). *Matrix: Sparse and Dense Matrix Classes and Methods*. doi:10.32614/CRAN.package.Matrix https://doi.org/10.32614/CRAN.package.Matrix, R package version 1.7-3, https://CRAN.R-project.org/package=Matrix.
- Gohel D, Skintzos P (2025). *flextable: Functions for Tabular Reporting*. doi:10.32614/CRAN.package.flexta https://doi.org/10.32614/CRAN.package.flextable, R package version 0.9.9, https://CRAN.R-project.org/package=flextable.
- Grolemund G, Wickham H (2011). "Dates and Times Made Easy with lubridate." *Journal of Statistical Software*, *40*(3), 1-25. https://www.jstatsoft.org/v40/i03/.
- Iannone R, Cheng J, Schloerke B, Hughes E, Lauer A, Seo J, Brevoort K, Roy O (2025). *gt: Easily Create Presentation-Ready Display Tables*. doi:10.32614/CRAN.package.gt https://doi.org/10.32614/CRAN.package.gt, R package version 1.0.0, https://CRAN.R-project.org/package=gt.
- Kurkiewicz D (2017). *docstring: Provides Docstring Capabilities to R Functions*. doi:10.32614/CRAN.package.docstring https://doi.org/10.32614/CRAN.package.docstring, R package version 1.0.0, https://CRAN.R-project.org/package=docstring.
- Lüdecke D (2024). *sjPlot: Data Visualization for Statistics in Social Science*. R package version 2.8.16, https://CRAN.R-project.org/package=sjPlot.
- Makowski D, Lüdecke D, Patil I, Thériault R, Ben-Shachar M, Wiernik B (2023). "Automated Results Reporting as a Practical Tool to Improve Reproducibility and Methodological Best Practices Adoption." *CRAN*. https://easystats.github.io/report/.
- Müller K, Wickham H (2025). *tibble: Simple Data Frames*. doi:10.32614/CRAN.package.tibble https://doi.org/10.32614/CRAN.package.tibble, R package version 3.3.0, https://CRAN.R-project.org/package=tibble.
- R Core Team (2025). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.
- Rich B (2023). *table1: Tables of Descriptive Statistics in HTML*. doi:10.32614/CRAN.package.table1 https://doi.org/10.32614/CRAN.package.table1, R package version 1.4.3, https://CRAN.R-project.org/package=table1.
- Rinker TW, Kurkiewicz D (2018). *pacman: Package Management for R*. version 0.5.0, http://github.com/trinker/pacman.
- Sera F, Armstrong B, Blangiardo M, Gasparrini A (2019). "An extended mixed-effects framework for meta-analysis." *Statistics in Medicine*, DOI: 10.1002/sim.8362. http://www.ag-myresearch.com/2019_sera_statmed.html.

- Wickham H (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. ISBN 978-3-319-24277-4, https://ggplot2.tidyverse.org.
- Wickham H (2023). *conflicted: An Alternative Conflict Resolution Strategy*. doi:10.32614/CRAN.package.conflicted https://doi.org/10.32614/CRAN.package.conflicted, R package version 1.2.0, https://CRAN.R-project.org/package=conflicted.
- Wickham H (2023). *forcats: Tools for Working with Categorical Variables (Factors)*. doi:10.32614/CRAN.package.forcats https://doi.org/10.32614/CRAN.package.forcats, R package version 1.0.0, https://CRAN.R-project.org/package=forcats.
- Wickham H (2023). *stringr: Simple, Consistent Wrappers for Common String Operations*. doi:10.32614/CRAN.package.stringr https://doi.org/10.32614/CRAN.package.stringr, R package version 1.5.1, https://CRAN.R-project.org/package=stringr.
- Wickham H, Averick M, Bryan J, Chang W, McGowan LD, François R, Grolemund G, Hayes A, Henry L, Hester J, Kuhn M, Pedersen TL, Miller E, Bache SM, Müller K, Ooms J, Robinson D, Seidel DP, Spinu V, Takahashi K, Vaughan D, Wilke C, Woo K, Yutani H (2019). "Welcome to the tidyverse." *Journal of Open Source Software*, *4*(43), 1686. doi:10.21105/joss.01686 https://doi.org/10.21105/joss.01686.
- Wickham H, François R, Henry L, Müller K, Vaughan D (2023). *dplyr: A Grammar of Data Manipulation*. doi:10.32614/CRAN.package.dplyr https://doi.org/10.32614/CRAN.package.dplyr, R package version 1.1.4, https://CRAN.R-project.org/package=dplyr.
- Wickham H, Henry L (2025). *purrr: Functional Programming Tools*. doi:10.32614/CRAN.package.purrr https://doi.org/10.32614/CRAN.package.purrr, R package version 1.1.0, https://CRAN.R-project.org/package=purrr.
- Wickham H, Hester J, Bryan J (2024). *readr: Read Rectangular Text Data*. doi:10.32614/CRAN.package.readr https://doi.org/10.32614/CRAN.package.readr, R package version 2.1.5, https://CRAN.R-project.org/package=readr.
- Wickham H, Vaughan D, Girlich M (2024). *tidyr: Tidy Messy Data*. doi:10.32614/CRAN.package.tidyr https://doi.org/10.32614/CRAN.package.tidyr, R package version 1.3.1, https://CRAN.R-project.org/package=tidyr.