# Probability of causation for multi-causal occupational disease compensation: A scoping review of methods and alternatives

Javier Mancilla-Galindo[a,*], Martijn A. H. Oude Voshaar[b], Lützen Portengen[a], David van Klaveren[b], Roel Vermeulen[a], Susan Peters[a]

[a] *Utrecht University, Institute for Risk Assessment Sciences, Utrecht, The Netherlands,*

[b] *Erasmus Medical Center, Department of Public Health, Rotterdam, The Netherlands,*

**Abstract**

**Background:** Diseases of multi-factorial etiology pose challenges for attributing causation to specific exposures. The *probability of causation (PoC)* is commonly used to determine whether a worker's cancer is more likely than not due to occupational exposure, but has limitations (e.g., not accounting for acceleration of cancer occurrence).

**Objectives:** To describe PoC methods applied for occupational lung cancer compensation (PoC review) and alternatives for compensating workers with multi-causal occupational diseases (Alternatives review).

**Sources of evidence:** PubMed and Embase were queried for both reviews (May 2025). The PoC review additionally searched OpenAlex with citation snowballing (n=1,697 records); CINAHL was additionally queried for the Alternatives review (n=329). No language restrictions were applied. Registered protocol: https://osf.io/9evsy.

**Charting methods:** Titles and abstracts were screened using ASReview. Data extracted included chemical/physical agent, PoC thresholds, uncertainty sources, and methodological improvements or alternatives for compensation.

**Results:** Fifteen studies were selected for the PoC review. Radiation was the most assessed agent (n=11), followed by asbestos (n=3), and coal-tar pitch (n=1). Thirteen studies applied a PoC threshold of 50%, using upper 95% (n=8) or 99% (n=2) confidence intervals to favor claimants. Main uncertainty sources: statistical error (n=10), population risk transfer (n=7), and exposure measurement error (n=6). The Alternatives review included 12 studies addressing mechanistic models of cancer development, years of life lost, and frameworks considering harm dimensions beyond binary compensation eligibility.

*Corresponding author

*Email address:* j.mancillagalindo@uu.nl (Javier Mancilla-Galindo)

**Conclusions:** PoC was applied for three of 20 established occupational lung carcinogens. Methodological improvements of PoC estimation and alternative methods could improve individualized compensation assessments.

*Keywords:* probability of causation, assigned share, cancer, causality, scoping review

---

## Key Messages

### What is already known on this topic

- Probability of causation (PoC) $\geq$ 50% (corresponding to a doubling of disease risk) is commonly applied as eligibility criterion for workers' compensation.
- In claimant-favorable applications, this threshold is evaluated against the upper bound of confidence or credible limits of the exposure-response relation to account for uncertainties in exposure-response estimation, but has also been suggested to compensate for other intrinsic limitations of the PoC, such as the inability to capture cancer acceleration and uncertainties in an individual claimant's lifetime exposure.

### What this study adds

- Uncertainty estimation when applying PoC for lung cancer has included Monte Carlo simulations for uncertain model parameters, risk transfer approaches for differences between source and target populations, and model averaging to address uncertainty in model specification. PoC estimation based on multi-stage clonal expansion models could account for cancer acceleration.
- Alternative measures and frameworks included expected years of life lost, consideration of functional, psychological, professional, and cancer-specific outcomes, and compensation systems operating with standards other than PoC $\geq$ 50%.

### How this study might affect research, practice or policy

- PoC estimation improvements and consideration of the different sources of uncertainty described in this review could be applied in compensation systems performing eligibility assessments based on causation plausibility.
- Specific disease harm assessment could be incorporated in compensation decisions to better account for the differential damages experienced by workers diagnosed with multi-causal occupational diseases.

## 1. Introduction

Occupational diseases can have multiple contributing causes, making it difficult to identify specific etiological factors and quantify their contributions in an individual case. Lung cancer is the most frequently diagnosed cancer and leading cause of cancer death globally.[1] Although family history increases lung cancer risk,[2] non-shared environmental factors explain most variation in its occurrence,[3,4] with known risk factors including smoking, occupational exposures, air pollution, and secondhand smoke.[5] Identifying the specific etiological factors and quantifying their contributions to lung cancer in an individual case therefore presents a significant methodological challenge, particularly in the context of tort law and compensation scheme eligibility (**Supplemental Box 1**).

According to Tian and Pearl, causation can be decomposed into probability of sufficiency and probability of necessity.[6] The first relates to the concept of medical causation as the existence of an active causal process capable of producing the consequence, whereas the latter indicates the absence of alternative processes that can explain the effect, which naturally couples with legal causation in tort law. The probability of necessity has thus been applied in occupational epidemiology as the **probability of causation (PoC)** (also *assigned share**) to estimate whether a health outcome was *more likely than not* caused by a single exposure. In one of the earliest and simplest approaches, the PoC is applied as a checklist for occupational contact dermatitis, where meeting a majority of predefined criteria (at least 4 out of 7) supports PoC >50%.[8] In other approaches, the attributable fraction is used to estimate whether the relative risk (RR) for the outcome is doubled (RR = 2).[9] When cumulative exposure is used, a common approach involves estimating the quantitative threshold at which PoC exceeds 50% (**Supplemental Box 2**).

In each of these approaches, PoC is derived from average, population-level estimates and then assigned to individual claimants, an inference valid only if that individual is truly representative of the underlying reference population.[10] Occupational exposures are rarely homogeneous between workers, even within the same job title or work area,[11] but homogeneity is frequently assumed since individual lifetime exposures are not commonly available. A claimant's true exposure may thus lie above or below the assigned average, over- or underestimating their PoC. Unmeasured differences in susceptibility between workers, and the failure to account for exposure accelerating disease onset, mean the PoC generally understates the true individual value.[9,10] Therefore, fixed eligibility thresholds such as PoC $\geq$ 50% can result in compensation being denied to

*Lagakos and Mosteller (1986)[7] proposed the name *assigned share* to relax the interpretation of cancer being caused by radiation, thus representing the *share* of excess risk attributed to the exposure, and *assigned* to reflect that multiple population reference sets were created for the USA National Institutes of Health, based on subgroups of sex, age at exposure and diagnosis, radiation dose, type of cancer, and smoking (for lung cancer), to which individual workers are assigned.

workers whose true PoC exceeds it while granting it to others whose true value lies below.[12] To counteract these limitations, uncertainties are often weighted to the individual's benefit in claimant-favorable approaches.[13,14,15]

No systematic guidance exists on how best to account for these uncertainties when applying the PoC for workers' compensation, and its limitations further motivate the search for alternative methods. Thus, this scoping review aimed to describe how the PoC has been applied for the financial compensation of workers who develop lung cancer, and to scope for methodological improvements or alternative methods for the compensation of workers who develop multi-causal diseases.

## 2. Methods

A pilot (October–December 2024) concluded that focusing on lung cancer rather than all cancer types yielded sufficient studies to gain insights into PoC applications, while significantly reducing workload. The protocol summarizing the pilot results was first published on https://github.com/UtrechtUniversity/PoC-scoping-review (5/12/2024) and registered in the Open Science Framework (5/06/2025).[16] PRISMA-ScR guidance for reporting was followed. This scoping review consists of two parts:

1. **PoC review**: A description of studies estimating the probability of causation from population-average exposure-response relations to assess whether occupational exposures caused lung cancer in individual workers.
2. **Alternatives to the PoC**: exploratory scoping review to identify methodological improvements to the PoC, or alternatives for workers' compensation.

#### *2.0.1. Eligibility criteria*

For the PoC review, the research question was framed according to the Population, Concept, Context (PCC) mnemonic:

- Population: Adults at risk of developing lung cancer due to workplace exposures.
- Concept: The estimation, application, or evaluation of the PoC based on a quantitative exposure-response relation to estimate the likelihood that a health outcome was caused by a chemical, physical, or biological workplace exposure.
- Context: Lung cancer and histological subtypes.

Both observational and experimental studies were eligible, and systematic reviews with meta-analysis. Case series were eligible if they reported the application of PoC obtained from studies with one of the prior designs. Case reports, narrative reviews, editorials, commentaries, and conference abstracts were excluded. Both peer-reviewed studies and pre-prints were considered for inclusion from inception. No language restrictions were applied during searching to avoid language publication bias.[17]

For the alternatives to the PoC, a complementary research question was defined as:

- Population: Workers with occupational diseases.
- Concept: Types of damages and reparation, including pecuniary (lost wages, financial loss, and pension) and immaterial damages (pain and suffering, quality of life, emotional harm, and life expectancy).

- Context: Workers' compensation systems.

Only peer-reviewed literature published after 2000 was considered for the review of alternatives, without restricting by article type or language.

#### *2.0.2. Information sources and search strategy*

Published studies were identified in PubMed and Embase for both reviews, supplemented with OpenAlex (PoC review) and CINAHL (Alternatives review). A detailed list of databases queried per interface and the search queries per database are provided in the **Supplemental Methods (section 1.1-1.2)**. Database searches were conducted on 13/05/2025. Studies identified in the PoC review then underwent backward and forward citation snowball retrieval in OpenAlex on 15/08/2025.

Retracted studies were excluded. Records were deduplicated with the Automated Systematic Search Deduplicator (ASySD) in R.[18]

#### *2.0.3. Selection of studies*

Translations were obtained for titles and abstracts, and full-text articles not in English, Spanish, Dutch, or German (see **Supplemental Methods section 1.3**). Titles and abstracts for the PoC review were screened using ASReview v.2.0.2.[19] Model configurations and stopping criteria[20] are described in the **Supplemental Methods (section 1.4-1.5)**. Screening was not assisted by ASReview for the alternatives review. Additionally, records from the PoC dataset were labelled as potentially relevant for the alternatives review, independently of their relevance to the PoC review.

All records identified as potentially relevant were sought for full-text retrieval. In the PoC review, studies were excluded if they did not estimate PoC, if lung cancer was not an outcome, or if PoC was not estimated from a quantitative exposure-response relation. Theoretical and narrative review articles discussing PoC estimation from quantitative relations were retained to prevent miscalibration of ASReview classification rules, and are only included for descriptive analyses. In the alternatives review, studies were excluded if they did not report a multi-causal health outcome or did not discuss an alternative to the PoC for compensation.

#### *2.0.4. Data extraction and synthesis*

General bibliographic data (authorship, publication year, language) and study type (theoretical/review, cohort, case-control, case-series, or meta-analysis) were obtained for all included records. For the PoC review, data extracted included: study design and population characteristics (general or specific worker population), agent type and assessment method, outcome definition

and measurement, source of the exposure-response function and excess risk estimator (e.g., incidence rate ratio, standardized mortality ratio), PoC threshold (e.g., $\geq 50\%$) and use of confidence or credibility intervals, sources of uncertainty discussed by authors, and underlying model assumptions (e.g, functional form, confounding adjustment). Equations for PoC estimation were recorded for epidemiological and theoretical/review studies.

For the alternatives review, data extraction was not pre-specified due to its exploratory nature. Studies were classified into methodological (studies proposing methods or theoretical frameworks) and compensation (studies describing compensation systems or damage assessment). For methodological studies, data extracted included: specific method, target outcome, data inputs (e.g., epidemiological data, sequencing data, clinical assessments), advantage over PoC, whether acceleration of cancer occurrence was accounted for, and key limitations. For studies addressing compensation frameworks, additional data included: compensation pathway (e.g., statutory workers' compensation, tort law), causation standard, damage dimensions assessed, burden of proof, key benefits, and funding mechanism.

Data was extracted by a single unblinded reviewer (JMG). The full descriptive analysis and synthesis methods are provided as **Supplemental Methods (section 1.6)**. All analyses and visualizations were conducted in R (version 4.5.1) via RStudio (version 2025.05.1+513). The datasets generated for this review, analysis code, and documentation are provided in the repository https://github.com/UtrechtUniversity/PoC-scoping-review.

## 3. Results

### *3.1. Part I. Probability of causation of lung cancer due to occupational agents*

The flow diagram of studies assessed for eligibility, screening, and final inclusion in the PoC review is presented in **Figure 1**.

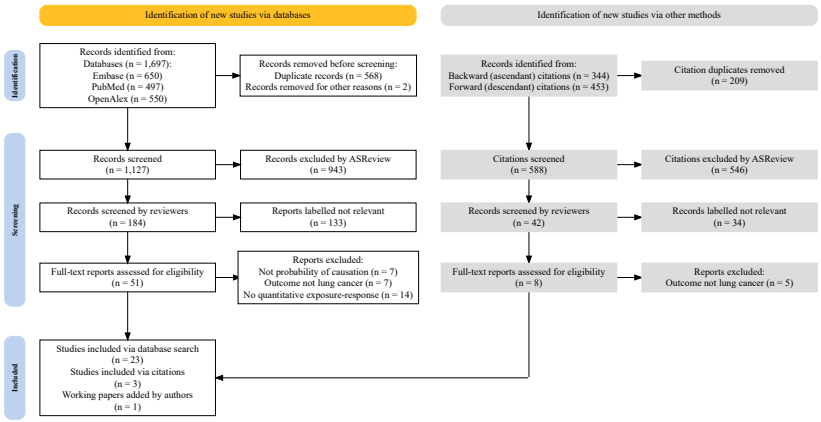



Figure 1: PRISMA flow diagram of studies assessed for eligibility and included for the PoC of lung cancer scoping review.

We included 27 studies published in English (n = 22), Japanese (n = 2), French (n = 1), Mandarin (n = 1), and Portuguese (n = 1). Theoretical and review articles (n = 12, references in **Supplement**) are included for descriptive analyses, together with epidemiological studies[21,22,14,23,24,25,26,27,28,29,30,31,13,32,33] (n = 15) for which additional data were extracted. The report by Coenen, et al.[14] was complemented by data available in an associated working manuscript.[33] The studies were published between 1984–2026 during decades 1980s (n = 4), 1990s (n = 6), 2000s (n = 6), 2010s (n = 6), and 2020s (n = 5), across countries shown in **Figure 2**, including: Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, India, Israel, Italy, Japan, the Netherlands, Poland, Romania, Russia, Slovakia, South Korea, Spain, Sweden, the USA, and the United Kingdom.




Figure 2: Map of countries of study participants (for research articles) and authors (for theoretical and review articles). No studies (or authors) based in Africa were found.

### *3.1.1. Epidemiological studies estimating or applying the PoC for lung cancer*

The characteristics of the individual epidemiological studies are presented in **Table 1**. Regarding the study design, studies included were cohorts[22,23,25,27,28,29,30,31,13,32] (n = 10), case-control studies[24] (n = 1), case series[21,26] (n = 2), and meta-analyses[14,33] (n = 2).

Table 1: Study characteristics of epidemiological studies estimating the probability of causation for lung cancer.

| Study | Language | Study design | Country | Worker population | Outcome | Outcome measurement | Exposure | Exposure measurement | Effect measure |
|---|---|---|---|---|---|---|---|---|---|
| Mancilla-Galindo et al., 2026 | English | Meta-analysis | Australia, Belgium, Canada, China, France, Italy, Sweden, United Kingdom, USA | Mining, production, and downstream asbestos industries (22 occupational studies: mines, mills, textile, friction products, asbestos cement, and insulation in the ECHA study base) | Lung cancer | Varies per study included in the systematic review | Asbestos | Study-specific job exposure matrices (JEMs) estimating lifetime cumulative asbestos exposure in fibre/ml-years. Measurement methods vary across studies and time periods. Exposure assessment quality rated low in 15/22 studies due to poor documentation, low exposure contrast, use of external conversion factors, or incomplete job histories. | Mixed: SMR (most cohort studies), OR, HR, RR |

Table 1: Study characteristics of epidemiological studies estimating the probability of causation for lung cancer. *(continued)*

| Study | Language | Study design | Country | Worker population | Outcome | Outcome measurement | Exposure | Exposure measurement | Effect measure |
|---|---|---|---|---|---|---|---|---|---|
| Coenen et al., 2024 | English | Meta-analysis | Canada, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, United Kingdom | General population (14 case-control studies); asbestos-exposed workers predominantly in downstream industries using asbestos products (e.g., construction, maintenance), rather than primary asbestos production | Lung cancer | Lung cancer with histological or cytological confirmation | Asbestos | Job-exposure matrix (SYN-JEM) estimating lifetime cumulative asbestos exposure in fibre-years (ff/ml-years), developed from 27,958 personal measurements (>95% phase contrast microscopy, <5% electron microscopy); assigns annual average exposure by job (ISCO-68), calendar year, and region | OR (interpretable as IRR) |
| Guidotti, 2002 | English | Cohort | USA | Various industries (textile workers set as high-exposed worker population) | Lung cancer | Insufficient information | Asbestos | Cumulative asbestos exposure (fibres/cm$^3$ · years) estimated from study-specific job-exposure matrices; original measurements predominantly from phase contrast microscopy (PCM) and particle counting (impinger) across different asbestos industries | SMR |

Table 1: Study characteristics of epidemiological studies estimating the probability of causation for lung cancer. *(continued)*

| Study | Language | Study design | Country | Worker population | Outcome | Outcome measurement | Exposure | Exposure measurement | Effect measure |
|---|---|---|---|---|---|---|---|---|---|
| Armstrong & Thériault, 1996 | English | Case-control | Canada | Aluminium smelter workers | Lung cancer | ICD-8 and ICD-9 codes from the Quebec Tumour Registry, industry records, and hospitals surrounding the plants. | Coal Tar Pitch Volatiles | Job exposure matrix that comprised estimates of exposure to benzene-soluble matter and benzo-a-pyrene for each job | OR |
| Ulanowski et al., 2020 | English | Cohort | Germany | General population | Lung cancer | ICD-10 codes from Germany disease registry | Radiation | Individual exposure history from facility-specific personal dosimetry records; cumulative organ dose in Sv. ProZES software applies risk models to these recorded doses | IRR |
| Sun et al., 2019 | Mandarin | Cohort | China | Radiation workers (occupationally exposed individuals under GBZ 97-2017) | Lung cancer | Diagnosis documented in medical records | Radiation | Cumulative organ dose (Sv) from annual occupational exposure records from individual monitoring programmes, estimated according to national dose estimation standards (GBZ 97-2017) | IRR |

Table 1: Study characteristics of epidemiological studies estimating the probability of causation for lung cancer. *(continued)*

| Study | Language | Study design | Country | Worker population | Outcome | Outcome measurement | Exposure | Exposure measurement | Effect measure |
|---|---|---|---|---|---|---|---|---|---|
| Kim et al., 2018 | English | Case-series | South Korea | Radiation workers (healthcare, nuclear power plant, non-destructive testing, semiconductor industry) | Lung cancer by histological subtype | Documented diagnosis in workers' compensation claims | Radiation | Cumulative organ dose (Sv) reconstructed from personal dosimetry records (film badges) documented in workers' compensation claim files | IRR |
| Djounova et al., 2014 | English | Cohort | Bulgaria | Nuclear power plant workers | Lung cancer | Periodical medical examinations; with ICD-10 coded diagnosis | Radiation | Personal dosimetry (individual dosimetric control system at Kozloduy NPP); cumulative effective dose in mSv from annual monitoring records. PoC calculated using Survrad software (IAEA, 1996), a risk calculation tool applying models to recorded dose data | IRR |
| Cucinotta, 2014 | English | Cohort | USA | Astronauts | Lung cancer | Background cancer rates from mortality records | Radiation | Organ dose equivalents estimated using computational radiation transport models of space radiation environments (galactic cosmic rays, trapped radiation belts, solar particle events) in spacecraft shielding and tissue; validated against flight dosimetry measurements | IRR |

Table 1: Study characteristics of epidemiological studies estimating the probability of causation for lung cancer. *(continued)*

| Study | Language | Study design | Country | Worker population | Outcome | Outcome measurement | Exposure | Exposure measurement | Effect measure |
|---|---|---|---|---|---|---|---|---|---|
| Kocher et al., 2008 | English | Cohort | USA | Energy workers (EEOICPA claimants, various occupations) | Lung cancer | Cancer diagnosis in compensation claim | Radiation | Facility-specific dose reconstruction from personal dosimetry records, area monitoring, bioassay, and workplace characterisation. | IRR |
| Jacobi, 1999 | English | Cohort | Germany | Underground uranium miners | Lung cancer | Claims submitted for compensation | Radiation | Job-exposure matrix combining area monitoring data of radon concentrations (measurements began 1955), job histories, and ventilation records; cumulative exposure in working level months (WLM). For earlier periods (1946–1955), exposures reconstructed from limited measurements and modelling assumptions | IRR |
| Land, 1995 | English | Case-series | Japan, USA | Underground uranium miners, general population | Lung cancer by histological subtype | Reviewed by panel of 8 pathologists, samples obtained through different material (autopsy, biopsy, surgical, other) | Radiation | For Japan (LSS): individual absorbed lung tissue dose estimated using DS86 dosimetry. For USA uranium miners: cumulative radon progeny exposure in working level months (WLM) from area monitoring in underground mines | IRR |

Table 1: Study characteristics of epidemiological studies estimating the probability of causation for lung cancer. *(continued)*

| Study | Language | Study design | Country | Worker population | Outcome | Outcome measurement | Exposure | Exposure measurement | Effect measure |
|---|---|---|---|---|---|---|---|---|---|
| Chmelevsky et al., 1994 | English | Cohort | Czech Republic | Underground uranium miners | Lung cancer | Multiple sources: National and district registries, oncological notifications to the health ministry, district hospitals anatomo-pathological records | Radiation | Personal dosimetrical cards recording area and personal measurements of radon progeny concentrations in underground mines; cumulative exposure in working level months (WLM, a unit defined as 170 working hours at 1 Working Level of radon progeny concentration) | IRR |
| Bhatia & Murthy, 1992 | English | Cohort | India | General population | Lung cancer | Insufficient information | Radiation | Hypothetical radiation dose values used for tabulation of PoC; not based on individual exposure measurements | IRR |
| Ichikawa et al., 1988 | Japanese | Cohort | Japan | General population | Lung cancer | Cancer registries from seven regions in Japan | Radiation | Hypothetical radiation dose values used for tabulation of PoC; not based on individual exposure measurements | IRR |

**Abbreviations:** DS86, Dosimetry System 1986; ECHA, European Chemicals Agency; EEOICPA, Energy Employees Occupational Illness Compensation Program Act; GBZ, Chinese national occupational health standard; HR, hazard ratio; IAEA, International Atomic Energy Agency; ICD, International Classification of Diseases; IRR, incidence rate ratio; JEM, job-exposure matrix; LSS, Life Span Study; NPP, nuclear power plant; OR, odds ratio; PCM, phase contrast microscopy; PoC, probability of causation; RR, relative risk; SMR, standardised mortality ratio; WLM, working level months.

Most studies assessed radiation[21,22,23,25,26,28,29,30,31,13,32] as the agent of interest (n = 11), followed by asbestos[14,27,33] (n = 3), and coal tar pitch volatiles[24] (n = 1). Various exposure assessment methods were used across studies. Job-exposure matrices were used in five studies.[14,24,28,27,33] Five studies relied on personal dosimetry or individual monitoring records.[21,22,23,29,25] Two studies used dose reconstruction combining multiple sources such as personal dosimetry, area monitoring, and bioassay.[13,26] One study estimated organ dose equivalents using computational radiation transport models.[30] Two studies used hypothetical dose values for tabulation of PoC rather than individual-level exposures.[31,32]

Outcome assessment also varied. Two studies estimated the PoC for lung cancer subtypes.[21,26] The remaining estimated the PoC for lung cancer as a single outcome. Specific outcome assessment methods were registry-based diagnoses using ICD codes,[23,24,22,32,30] histological or cytological confirmation,[14] compensation claims,[21,28,13] medical records,[29] and varied in a meta-analysis.[33] Chmelevsky, et al.[25] used multiple sources including national registries and hospital records without further specification, and two studies did not provide sufficient detail on outcome ascertainment.[27,31]

Most studies (n = 13) used a PoC threshold of 50% for compensation purposes.[21,14,23,24,25,26,27,28,29,30,31,13,33] Five studies reported specific numerical exposure cutoff values corresponding to a PoC $\geq$ 50% (e.g., 4.3 to 40 fibre/cm$^3$-years for asbestos,[14,27,33] 100 ~$\mu$g/m$^3$-years benzo[$a$]pyrene,[24] and 250 Sv-months for radiation.[28] Eight studies provided subgroup-specific thresholds (e.g., varying by age, sex, exposure duration, or diagnosis) rather than fixed cutoff values.[21,23,25,26,29,30,31,13] The remaining two studies did not report specific lung cancer PoC compensation thresholds.[22,32]

### *3.1.2. Uncertainties*

The different thresholds for the PoC and consideration of uncertainties per study are presented in **Table 2**. To account for uncertainty in exposure-response relations, eight studies used the upper bound of the 95% confidence limit when estimating PoC,[22,14,23,24,29,30,21,33] of which two used 95% prediction intervals[14,33] to additionally account for between-study heterogeneity. Others used 90%[31] or 99%[13] credible intervals. Kim, et al.[21] used 99% confidence intervals in addition to 95% when exposure measurement error was suspected. Two studies did not report the use of upper bounds in PoC estimations[25,26,27,28,32]

The main sources of uncertainty in exposure-response relations recognized by authors were statistical error (n = 10),[24,14,22,21,23,29,30,31,13,33] differences in target population requiring risk transfer (n = 7),[21,23,29,30,31,13,32] correct model specification (n = 7),[24,31,30,27,32,23,29] measurement error (n = 6),[21,14,28,30,13,33] bias (n = 4),[24,30,27,33] between-study heterogeneity (n = 2),[14,33] and repeated agent exposures in different periods (n = 2).[28,32]

A variety of ways of addressing uncertainties were implemented per study. In one of the earlier studies by Ichikawa, et al.,[32] uncertainties related to smok-

ing, model linearity, age at exposure, and repeated agent exposure were not incorporated into models due to poor understanding of their role. Population risk transfer was addressed through approaches including risk transfer functions with uncertainty distributions[23,29,31] and random linear combination models.[21] Uncertainty of (incorrect) model specification was handled through model averaging (multi-model inference) in 2 studies[23,29] to weight different functional forms, including additive versus multiplicative effects of smoking and radiation, whereas Armstrong, et al.[24] opted for a pragmatic preference for multiplicative models, as models assuming interaction resulted in under-compensation of cancers plausibly caused by benzo[*a*]pyrene in smokers. Jacobi, et al.[28] addressed multiple repeated exposures at different time periods as additive in the PoC scale. Sun, et al.[29] additionally incorporated lung cancer latency and smoking adjustment factors, while one study[23] used the distribution of smoking habits in the German population when smoking status was unreported. Three studies applied Monte Carlo simulations to incorporate uncertainty distributions in PoC estimates.[21,30,13]

Table 2: Consideration of uncertainties in occupational studies estimating the PoC of lung cancer.

| Study | Exposure | PoC threshold | Upper bound | Exposure threshold | Uncertainties | Uncertainty description |
|---|---|---|---|---|---|---|
| Mancilla-Galindo et al., 2026 | Asbestos | 0.5 | Upper 95% prediction intervals | • 18.2 fibre/cm$^3$-years (upper 95% PI)<br>• 62.9 fibre/cm$^3$-years (point estimate) | Statistical error, measurement error, between-study heterogeneity, confounding (most studies unadjusted for smoking), exposure assessment quality variation | Upper 95% prediction intervals of exposure-response used for compensation to account for between-study heterogeneity and study design issues estimated attenuate exposure-response by factor 1.5-2, only 2/22 studies adjusted for smoking. |
| Coenen et al., 2024 | Asbestos | 0.5 | Upper 95% prediction intervals | • 4.3 fibre/cm$^3$-years (upper 95% prediction interval)<br>• 10.5 fibre/cm$^3$-years (point estimate) | Statistical error, measurement error (Berkson-type from JEM), between-study heterogeneity | Upper 95% prediction intervals of exposure-response when estimating PoC to account for between-study heterogeneity. Berkson-type measurement error from group-level JEM exposure assignment results in wider confidence intervals but unbiased point estimates. |
| Guidotti, 2002 | Asbestos | 0.5 | Point estimates only | 40 fibre/cm$^3$-years | Bias (confounding), correct model specification (linear vs non-linear) | Exposure-response from the highest risk population used to compensate for mentioned uncertainties |
| Armstrong & Thériault, 1996 | Coal Tar Pitch Volatiles | 0.5 | Upper 95% confidence intervals | • 45.9 $\mu$g/m$^3$-years benzo[$a$]pyrene (upper 95% confidence interval)<br>• 100 $\mu$g/m$^3$-years benzo[$a$]pyrene (point estimate) | Statistical error, correct model specification (linear vs non-linear, multiplicative vs additive), bias (confounding and information) | Upper 95% confidence interval adopted by compensation board. A multiplicative model is preferred as the additive model undercompensates cases with plausibly high exposures due to qualifying thresholds increasing with smoking history. |

Table 2: Consideration of uncertainties in occupational studies estimating the PoC of lung cancer. *(continued)*

| Study | Exposure | PoC threshold | Upper bound | Exposure threshold | Uncertainties | Uncertainty description |
|---|---|---|---|---|---|---|
| Ulanowski et al., 2020 | Radiation | 0.5 | Upper 95% confidence intervals | Subgroup-specific: depends on exposure history, sex, age, birth year, and smoking status | Statistical error, correct model specification, population, unknown smoking status | Upper 95% confidence intervals derived from multi-model inference (model averaging across different exposure-response specifications). Population transfer uncertainty modelled stochastically assuming baseline ratio log-uniformly distributed. Smoking uncertainty modelled using population distribution of smoking habits when individual status unknown. |
| Sun et al., 2019 | Radiation | 0.5 | Upper 95% confidence intervals | Subgroup-specific: depends on cumulative dose, sex, age at exposure, age at diagnosis, exposure duration, smoking status, and latency | Statistical error, correct model specification (additive vs multiplicative), population transfer, latency, smoking adjustment factor | Upper 95% confidence interval used for compensation. Multi-model inference (model averaging) for model specification uncertainty. Population transfer uncertainty from Japanese to Chinese population. Post-estimation adjustments for lung cancer latency and smoking adjustment factor. |
| Kim et al., 2018 | Radiation | 0.5 | Upper 95%, 99% confidence intervals | Subgroup-specific: depends on cumulative dose, cancer type, sex, age at exposure, and attained age | Statistical error, measurement error, population transfer | Upper 99% confidence interval used as decision threshold. Population transfer uncertainty adjusted using random linear combination model. Dosimetry measurement error accounted for through systematic and random error corrections. Uncertainties combined using Monte Carlo simulation. |
| Djounova et al., 2014 | Radiation | Not stated | Upper 95% confidence intervals | Subgroup-specific: depends on cumulative dose, age at exposure, and sex | Statistical error | Upper 95% confidence interval reported for PoC estimates. No additional uncertainty quantification beyond statistical error. |

Table 2: Consideration of uncertainties in occupational studies estimating the PoC of lung cancer. *(continued)*

| Study | Exposure | PoC threshold | Upper bound | Exposure threshold | Uncertainties | Uncertainty description |
|---|---|---|---|---|---|---|
| Cucinotta, 2014 | Radiation | 0.5 | Upper 95% confidence intervals | Subgroup-specific: depends on organ dose equivalent, tissue type, age at exposure, sex, and space mission duration | Statistical error, measurement error, bias (selection), population transfer, correct model specification (additive vs multiplicative) | Upper 95% confidence intervals reported for PoC. Monte Carlo simulation jointly modeling pre-specified distributions for: radiation quality factor (greater biological damage of space radiation), the dose and dose-rate effectiveness factor, uncertainty in exposure-response (statistical error, selection bias, and measurement error), and weights mixing additive and multiplicative risk-transfer models. |
| Kocher et al., 2008 | Radiation | 0.5 | Upper 99% credible intervals | Subgroup-specific: depends on age of onset, duration and age of diagnosis, and probability distribution of unknown parameters | Statistical error, measurement error, population transfer | Upper 99% credibility limit used for compensation decisions. Monte Carlo simulations incorporating probability distributions for: dosimetry measurement error, population transfer, dose-rate effectiveness factor. Outcome misclassification and time-period extrapolation of risks are recognized. |
| Jacobi, 1999 | Radiation | 0.5 | Point estimates only | 250 Sv-months | Measurement error, repeated exposure periods | Repeated occupational exposures assumed additive on the PoC scale. Partial compensation possible at PoC threshold of 20%. Measurement error in retrospective exposure reconstruction from limited early monitoring data. |
| Land, 1995 | Radiation | 0.5 | Not reported | Subgroup-specific: depends on cumulative exposure, lung cancer cell type, age at diagnosis, sex, smoking history, and population | - | - |

Table 2: Consideration of uncertainties in occupational studies estimating the PoC of lung cancer. *(continued)*

| Study | Exposure | PoC threshold | Upper bound | Exposure threshold | Uncertainties | Uncertainty description |
|---|---|---|---|---|---|---|
| Chmelevsky et al., 1994 | Radiation | 0.5 | Not reported | Subgroup-specific: depends on age of onset, duration and diagnosis age | - | - |
| Bhatia & Murthy, 1992 | Radiation | 0.5 | Upper 90% credible intervals | Subgroup-specific: depends on dose, sex, age at exposure, and cancer type | Statistical error, population transfer, correct model specification (additive vs multiplicative) | Upper 90% credibility limits reported. Population transfer uncertainty from Japanese to Indian population explored under additive and multiplicative models. |
| Ichikawa et al., 1988 | Radiation | Not stated | Point estimates only | Subgroup-specific: depends on age of onset, duration and diagnosis age-specific | Population transfer, correct model specification (linear vs non-linear), age at exposure, repeated exposure periods, and smoking | Uncertainties from population risk transfer, model specification (linear vs non-linear), age-at-exposure effects, lack of consideration of smoking in models, and repeated exposure periods were acknowledged but not formally incorporated into models. |

**Abbreviations:** JEM, job-exposure matrix; PoC, probability of causation.

### *3.2. Part II. Methodological improvements to the PoC and alternatives for workers' compensation*

Studies assessed for eligibility, screening, and final inclusion in the review of alternatives to the PoC are shown in **Supplemental Figure 1**. In summary, 257 deduplicated records were screened from database searches (Embase, PubMed, and CINAHL), of which 4 studies[34,35,36,37] were included. An additional 8 studies were included from the PoC review dataset,[38,30,39,40,41,10,42,43] resulting in 12 studies in total. Of these, 6 addressed PoC methodological improvements or alternative measures and 6 described cancer damages and compensation frameworks. Details of individual studies and findings are presented **Supplemental Tables 2–3**

The methodological studies (**Table 3**) considered incorporation of exposure-outcome mediation information to reduce the uncertainty bounds of PoC,[43] mechanistic evidence integration,[42] mechanistic model specification,[10] clonal expansion models estimating the probability of harm,[39] and expected years of life lost.[38,30] Of these, 4 accounted for acceleration of cancer occurrence due to exposure. The remaining studies described statutory PoC-based systems,[40] alternative causation standards,[41] no-fault schemes,[36] medico-legal damage frameworks (**Supplemental Figure 2**),[34] and documented uncompensated damages in existing systems.[35,37] Details of individual study methods and findings are presented in **Supplemental Tables 2–3** and are commented in the Discussion section.

Table 3: Methodological alternatives and extensions to the probability of causation.

| Study | Approach | Method description | Key data inputs | Accounts for acceleration | Advantage over PoC | Key limitations |
|---|---|---|---|---|---|---|
| Robins & Greenland, 1991 | Years of life lost | Demonstrates that unconditional expected years of life lost is identifiable from cohort data, whereas age-specific and cause-specific expected years of life lost are not; proposes payment schemes proportional to expected years of life lost | Cohort data (rate ratios, survival functions) | Yes | • Provides an alternative compensation metric (years of life lost) that is more robust to model misspecification than PoC<br>• Accounts for both whether exposure caused death and how many years were lost | • Age-specific expected years of life lost not identifiable<br>• Requires unbiased cohort study<br>• Depends on biological mechanism assumptions for individual estimates |
| Cucinotta, 2014 | Years of life lost | NASA Space Cancer Risk model with Monte Carlo simulation; reports tissue-specific expected years of life-loss for astronauts; also reports PoC with 95% CI for specific cancers | Radiation doses from space missions, risk models, Monte Carlo uncertainty distributions | Yes | • Provides expected years of life-loss estimates per cancer type, averaging across multiple biological mechanisms and population risk transfer models<br>• Complements binary PoC with continuous severity measure | • Large uncertainties due to lack of human data for HZE particle radiation<br>• Qualitative differences in tumor lethality not fully accounted for |
| Eidemüller et al., 2023 | Two-stage colonal expansion (TSCE) model / probability of harm | Defines association measures: probability of association (PA), probability of harm (PH = newly induced + accelerated), probability of earlier harm (PEH = accelerated only); uses Monte Carlo simulations tracking individual cells through two-stage clonal expansion models with initiation and/or promotion mechanisms | TSCE model parameters derived from epidemiologic data, Monte Carlo cell-level simulations | Yes | • Shows that assigned share (AS) underestimates association when radiation acts through promotion (clonal expansion acceleration)<br>• Probability of harm can be substantially larger than AS | • Results depend on TSCE model assumptions (constant baseline parameters)<br>• Only two-stage models considered<br>• Difficult to separate initiating vs. promoting effects<br>• Not yet applied to occupational settings |

Table 3: Methodological alternatives and extensions to the probability of causation. *(continued)*

| Study | Approach | Method description | Key data inputs | Accounts for acceleration | Advantage over PoC | Key limitations |
|---|---|---|---|---|---|---|
| Beyea, 1999 | Mechanistic model specification | Demonstrates that different biologic models produce different PoC values from identical epidemiologic data and exposure-response relations | Epidemiological data, biological model assumptions | Yes | • Demonstrates that PoC is not identifiable from epidemiologic data alone<br>• Different biologic models yield different PoC for the same data, requiring explicit model specification | • No single correct model can be determined from epidemiologic data alone<br>• Model choice introduces irreducible uncertainty |
| Caravagna et al., 2016 | Mechanistic evidence (genomic) | PiCnIc pipeline: reconstructs cancer progression pathways from genomic data; distinguishes driver from passenger mutations and identifies mutually exclusive causal pathways | Cross-sectional next-generation sequencing data | No | • Enables retrospective assessment of mutation sequences that caused cancer<br>• Distinguishes causally relevant (driver) from correlated (passenger) alterations | • Requires cross-sectional population-level sequencing data<br>• Does not yet link mutations to specific exposures<br>• Substantial intertumor heterogeneity |
| Dawid, 2017 | Mediation-based PoC bounds | Shows that PoC can typically only be bounded (not point-identified) from population data; demonstrates how mediator and covariate information can narrow these bounds; complete mediators allow more precise inference than partial mediators | Experimental and/or observational data on exposure, outcome, confounders, and mediators | No | Provides formal framework for tightening PoC bounds using mechanistic information (mediators, covariates, sufficient covariates) | • Requires measurement of mediator variables<br>• Complete mediation assumption is strong<br>• Empirical application remains challenging |

**Abbreviations:** AS, assigned share; HZE, high atomic number and energy (particles); NASA, National Aeronautics and Space Administration; PoC, probability of causation; TSCE, two-stage clonal expansion.

## 4. Discussion

This scoping review describes the estimation of probability of causation (PoC) based on quantitative exposure-response relations for compensating workers with (lung) cancer. We selected 15 epidemiological studies for the PoC review. Noteworthy, PoC estimates considered only 3 occupational lung carcinogens out of the 20 with sufficient evidence of carcinogenicity in humans.[†] While this suggests that most agents remain understudied through this approach, it could also reflect that PoC estimation for other lung carcinogens are not communicated in the academic literature. Our complementary exploratory review included 12 studies addressing methodological improvements or alternatives for multi-causal disease compensation, including mechanistic models of cancer progression (e.g., clonal expansion models), years of life lost, and medico-legal frameworks that consider harm dimensions beyond binary eligibility determination for compensation.

#### *4.0.1. Uncertainties and methodological improvements to the PoC*

The studies included in the PoC review reflect that incorporating uncertainties into PoC estimation is a recurrent topic, especially since more recent studies[29,23] have incorporated multiple model parameter uncertainty distributions (e.g., exposure assessment, population risk transfer) through Monte Carlo simulations. The Interactive RadioEpidemiological Program (IREP), for instance, allows users to input probability distributions when the exact radiation equivalent dose is unknown, with further adjustment factors applied for systematic and random dosimetric error, yielding claimant-favorable assessments via the upper 99% credibility limit to estimate PoC.[13]

In the Dutch worker's compensation system for lung cancer due to asbestos,[14,33] uncertainty in individual exposure estimates from a job-exposure matrix is weighted in favor of the claimant through a default bandwidth factor.[15] Uncertainty in exposure-response estimation is addressed using 95% prediction intervals from meta-analyses, with the upper interval defining the threshold at which asbestos plausibly caused lung cancer.[33] Prediction intervals account for both sampling uncertainty and between-study heterogeneity, and can be interpreted at the individual level as the effect size for a randomly sampled subject from the population.[46]

Several reviewed studies applied external exposure-response relations requiring population risk transfer functions, most commonly in radiation studies transferring excess relative risks from the Japanese Life Span Study.[13,31,23] Approaches

[†]Loomis, et al.,[44] classified 19 agents (excluding occupation, industry or processes) as occupational lung carcinogens based on the International Agency for Research on Cancer (IARC) Monographs 1-120 (1971-2017). Acrylonitrile has since been included in the IARC list of classifications by cancer sites.[45]

include modeling risk transfer as random linear combinations of multiplicative and additive models,[13,23] cancer-specific fixed weights,[29] or comparisons across populations.[31] While these account for baseline rate differences between source and target populations, the underlying sampling assumptions remain implicit. Making these more explicit through covariate-based sampling weights[47] could improve future PoC estimations.

A related limitation is that none of these approaches account for temporal changes in competing risks within the target population, as baseline rates and mortality patterns may shift between the period for which the exposure-response relation was estimated and its application for compensation. Kocher et al.[13] acknowledge that IREP assumes constant baseline cancer incidence rates, which may bias PoC estimates when diagnosis occurs outside the reference period. As competing causes of death decline, workers survive longer and accumulate more person-time at ages when agent-related cancers manifest, potentially altering observed exposure-response relations in ways that depend on the underlying mechanism. Methodological work on attributable fractions has shown that competing risks and the choice of at-risk population can substantially affect such estimates.[48] Cucinotta et al. provide indirect support for this, showing that in never-smoker populations lower background rates reduce risk estimates for smoking-related sites whereas longer lifespans raise them for cancers manifesting at older ages such as prostate and breast.[49] For several smoking-related sites, lower background rates conversely raise PoC even as the mortality-risk estimate falls, since PoC is governed by the excess relative risk at diagnosis.[30] Future studies could examine how shifts in baseline rates and competing risks affect PoC estimates and consider risk transfer approaches reflecting the period and population in which compensation is being decided.

Lack of knowledge of the correct model form (mainly linearity and additive vs. multiplicative interaction) has been addressed through model averaging, in which "several models can be ranked and weighted to provide a quantitative measure of relative support for each competing hypothesis".[50] Stabilini et al. applied this approach by identifying eleven published excess relative risk models for solid cancers due to radiation and performing multi-model inference to derive a composite model, followed by Monte Carlo simulations to quantify estimation uncertainty.[51] Limitations include that model selection based on information criteria (AIC, BIC) can favor overfitted models[52] or counterintuitively penalize models with stratified baseline risk for relevant variables (e.g., sex, age).[51] Causal discovery models offer a novel approach when optimal model parameter forms are unknown;[53] howver, their black-box nature hinders interpretation and stakeholder communication.

Importantly, the choice of additive vs multiplicative models has direct equity consequences for compensation. As noted by Armstrong, et al.,[24] additive models (i.e., assuming interaction between agent and smoking) of lung cancer due to coal tar pitch volatiles systematically yielded lower PoC estimates for smokers, even when exposed to levels plausibly related to disease in non-smokers, result-

ing in undercompensation of smokers. Olsson, et al.[54] recently observed only small deviations from both scales for pairwise interactions between occupational carcinogens and smoking, supporting additive attribution as a pragmatic and claimant-protective approach.

#### *4.0.2. Narrowing PoC bounds through mechanistic evidence*

A fundamental limitation of PoC is that, without further assumptions, it generally cannot be point-identified from population data alone but only bounded within a range of compatible values.[43] For non-monotonic exposures such as radiation, the classical doubling-of-risk rule corresponds to the lower bound, so causation can be neither established nor ruled out when the relative risk is below 2. This range collapses to a single value under monotonicity (i.e., exposure can cause but never prevent the outcome), usually defensible for occupational carcinogens such as asbestos. When monotonicity cannot be assumed, Dawid et al.[43] showed the range can be narrowed by incorporating mediator information along the causal pathway. Building on this, Rubinstein et al.[55] decomposed PoC into direct and indirect pathway components under monotonicity, in principle allowing exposure-induced cancers to be distinguished from those arising through pathways coinciding with competing causes such as smoking. A related approach by Caravagna et al.[42] links exposure-specific mutational signatures to individual cases via cancer progression models, although Díaz-Uriarte and Johnston[56] caution that inferences from bulk-sequenced data may not transfer to the single-cell or tumor level, analogous to ecological inference in epidemiology.

The main limitation of these methods is that standard compensation data rarely support the identification assumptions they require, with adequate data on exposure, mediator, outcome, and confounders often unavailable. In tort law cases relying on causal interpretation, they could nonetheless refine individual attribution when assumptions are defensible and documentation is robust. In no-fault workers' compensation systems, where strict causal interpretation is not always required (see **Supplemental Box 1**), cancer progression pathway approaches within prediction and worker stratification frameworks as described by Díaz-Uriarte and Johnston[56] could be of interest. Prospective biomarker data collection in exposed workers could enable future applications.

#### *4.0.3. Models accounting for cancer acceleration: probability of harm and years of life lost*

A related reason PoC can only be interpreted as a lower bound is that it does not account for exposure-accelerated outcome occurrence.[9] Beyea and Greenland[10] further argued that PoC should only be used alongside an explicit biological model of outcome occurrence, demonstrating that different biologic models produce different PoC values from identical epidemiologic data. Building on this, Eidemüller et al.[39] proposed the probability of harm as an alternative

measure incorporating assumptions about cancer progression through multi-stage clonal expansion (MSCE) models. Their approach defines distinct association measures for newly induced, accelerated, and delayed cancers, using Monte Carlo simulations tracking individual cells through two-stage clonal expansion processes. For promotion models, where radiation accelerates clonal expansion of pre-cancerous cells, the probability of harm was substantially higher than the assigned share from classical radioepidemiological models. MSCE models have been applied to lung cancer due to asbestos and silica,[57,58] highlighting potential for broader occupational application, though assumptions on cell transition to cancer are strong and the choice between initiation and promotion mechanisms is difficult to resolve empirically.

Another approach reframes harm in terms of life lost rather than binary cancer occurrence. Robins and Greenland[59,38] demonstrated that while age-specific expected years of life lost is not identifiable from epidemiological data alone, the unconditional expected years of life lost among all exposed subjects can be consistently estimated from a cohort study. For an individual dying at a given time, this equals the probability that death was caused by exposure multiplied by remaining life expectancy without exposure, a continuous harm measure complementing binary PoC. Cucinotta[30] applied this framework to astronauts exposed to space radiation, reporting substantial variation in life-loss expectancy across cancer types. Despite being proposed decades ago, this approach has not been applied to lung cancer compensation, likely because it requires high-quality exposure and confounder data in representative cohorts with sufficient follow-up. Recent advances in predicting loss of life expectancy at cancer diagnosis[60] open new possibilities, as individualized estimates conditional on patient and tumor characteristics could substitute for the cohort-level life expectancy term and make the measure operational for individual claimants.

#### *4.0.4. Frameworks considering specific cancer impacts and damages*

Beyond quantifying causation, our alternatives review identified studies concerned with *which* harms should be compensated once an occupational cancer is recognized. Hérin, et al.[34] proposed a medico-legal framework (**Supplemental Figure 2**) based on the French "Dintilhac" nomenclature, distinguishing temporary damages occurring before disease consolidation from permanent damages arising afterwards, and covering four dimensions: functional limitations (graded on a 5-category incapacity scale), pain and psychological suffering, professional losses, and cancer-specific consequences such as aesthetic, sexual, recreational, or personal-assistance needs. Such multi-dimensional frameworks contrast with documented gaps in existing systems: Whiteman Jr.[37] found that pain and suffering are generally not compensable in US workers' compensation, and Lax and Klein[35] reported that most of injured workers experienced loss of health insurance, unreimbursed medical expenses, depletion of savings, and psychological distress that remained uncompensated.

Compensation systems also differ in the causation standards they apply. The

US Energy Employees Occupational Illness Compensation Program Act combines a PoC $> 50\%$ threshold (upper 99% confidence limit) with lump-sum payments, wage-loss benefits, and medical coverage,[40] illustrating how a PoC-based eligibility rule can coexist with broader damage compensation. Quebec's compensation system, analysed by Lippel,[41] explicitly rejects the 50% threshold, requiring instead that occupational exposure be "more probable than not" a contributing (not necessarily principal) cause. For disease–exposure pairs listed in the statute, causation is legally presumed and the burden shifts to the employer to disprove the occupational origin. Looker and Kelly[36] reviewed 19 vaccine-injury compensation schemes and found that some require less stringent causal evidence than PoC. For instance, the USA presumes causation for listed vaccine–adverse-event pairs occurring within specified time windows, and New Zealand compensates adverse events without requiring any causal determination. These examples show that viable no-fault schemes can operate with causation standards other than PoC $> 50\%$.

#### *4.0.5. Strengths and Limitations*

Strengths of this study include a broad search across PubMed, Embase, OpenAlex, and CINAHL, complemented by citation snowballing, with wide coverage of peer-reviewed literature. No language restrictions were applied, and multilingual screening models were used to identify complex patterns across languages, enabling inclusion of studies in five languages. The review linked methodological improvements in PoC estimation with compensation systems and damage frameworks, synthesizing uncertainty sources and model assumptions across diverse exposures. Datasets, code, and documentation were made openly available, supporting transparency and reproducibility.

Among the limitations, screening and charting were performed by a single reviewer. Data extraction was pre-specified for the PoC review but exploratory for the alternatives review. Since screening was assisted by ASReview,[19] the reviewer manually screened only ~15% of total eligible records for the PoC review; some relevant records may therefore have been missed. This risk was mitigated by applying different assisted learning models at successive screening stages. While database coverage of peer-reviewed literature was broad, PoC applications reported only in administrative or legal sources may have been missed.

## 5. Conclusion

Workers' compensation approaches based on the probability of causation (PoC) should account for the different sources of uncertainty in their estimation, with numerous potential improvements described in this review. Nonetheless, when anchored to binary eligibility decisions, the differential damage experienced by

workers with cancer may be overlooked, such as cancer acceleration and decreased quality of life, among other traditionally uncompensated harms. Incorporating mechanistic data on cancer progression into PoC estimation, or compensating based on broader harm dimensions may improve individualized causation assessments for multi-causal occupational disease compensation.

*Author contributions*

Javier Mancilla-Galindo: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. Martijn A. H. Oude Voshaar: Writing – review & editing. Lützen Portengen: Writing – review & editing. David van Klaveren: Funding acquisition, Project administration, Writing – review & editing. Roel Vermeulen: Conceptualization, Funding acquisition, Resources, Writing – review & editing. Susan Peters: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

*Acknowledgements*

None.

*Funding*

This study is part of the Lexces work program, which is funded by the Dutch Ministry of Social Affairs and Employment. The Institute for Risk Assessment Sciences (Utrecht University) participates in the Lexces collaboration (https://www.lexces.nl/en).

*Ethics statement*

Not applicable.

*Competing interests*

None reported.

*Data and code availability*

The datasets generated for this work, source code for this manuscript, statistical analysis code, and project documentation is available through the online repository: https://github.com/UtrechtUniversity/PoC-scoping-review.

*AI-use statement*

Claude (Anthropic) was used to assist with rephrasing text and improving English grammar and style throughout this manuscript. All AI-generated content was reviewed and edited by the authors, who take full responsibility for the final content.

## References


[1] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R. L. Siegel, I. Soerjomataram, A. Jemal, Global cancer statistics 2022: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA: A Cancer Journal for Clinicians 74 (3) (2024) 229–263. doi:10.3322/caac.21834.

[2] M. L. Coté, M. Liu, S. Bonassi, M. Neri, A. G. Schwartz, D. C. Christiani, M. R. Spitz, J. E. Muscat, G. Rennert, K. K. Aben, et al., Increased risk of lung cancer in individuals with a family history of the disease: A pooled analysis from the international lung cancer consortium, European Journal of Cancer 48 (13) (2012) 1957–1968. doi:10.1016/j.ejca.2012.01.038.

[3] P. Lichtenstein, N. V. Holm, P. K. Verkasalo, A. Iliadou, J. Kaprio, M. Koskenvuo, E. Pukkala, A. Skytthe, K. Hemminki, Environmental and heritable factors in the causation of cancer — analyses of cohorts of twins from sweden, denmark, and finland, New England Journal of Medicine 343 (2) (2000) 78–85. doi:10.1056/NEJM200007133430201.

[4] L. A. Mucci, J. B. Hjelmborg, J. R. Harris, K. Czene, D. J. Havelick, T. Scheike, R. E. Graff, K. Holst, S. Möller, R. H. Unger, et al., Familial risk and heritability of cancer among twins in nordic countries, JAMA 315 (1) (2016) 68. doi:10.1001/jama.2015.17703.

[5] A. Leiter, R. R. Veluswamy, J. P. Wisnivesky, The global burden of lung cancer: current status and future trends, Nature Reviews Clinical Oncology 20 (9) (2023) 624–639. doi:10.1038/s41571-023-00798-3.

[6] J. Tian, J. Pearl, Probabilities of causation: Bounds and identification, Annals of Mathematics and Artificial Intelligence 28 (1-4) (2000) 287–313. doi:10.1023/A:1018912507879.

[7] S. W. Lagakos, F. Mosteller, Assigned Shares in Compensation for Radiation-Related Cancers, Risk Analysis 6 (3) (1986) 345–357. doi:10.1111/j.1539-6924.1986.tb00227.x.

[8] C. G. Toby Mathias, Contact dermatitis and workers' compensation: Criteria for establishing occupational causation and aggravation, Journal of the American Academy of Dermatology 20 (5, Part 1) (1989) 842–848. doi:10.1016/S0190-9622(89)70096-7.

[9] S. Greenland, Relation of probability of causation to relative risk and doubling dose: a methodologic error that has become a social problem., American Journal of Public Health 89 (8) (1999) 1166–1169. doi:10.2105/AJPH.89.8.1166.

[10] J. Beyea, S. Greenland, The importance of specifying the underlying biological model in estimating the probability of causation:, Health Physics 76 (3) (1999) 269–274. doi:10.1097/00004032-199903000-00008.

[11] D. Loomis, H. Kromhout, Exposure variability: Concepts and applications in occupational epidemiology, American Journal of Industrial Medicine 45 (1) (2004) 113–122. doi:10.1002/ajim.10324.

[12] L. A. Cox, Probability of Causation and the Attributable Proportion Risk, Risk Analysis 4 (3) (1984) 221–230. doi:10.1111/j.1539-6924.1984.tb00142.x.

[13] D. C. Kocher, A. I. Apostoaei, R. W. Henshaw, F. O. Hoffman, M. K. Schubauer-Berigan, D. O. Stancescu, B. A. Thomas, J. R. Trabalka, E. S. Gilbert, C. E. Land, Interactive radioepidemiological program (IREP): A web-based tool for estimating probability of causation/assigned share of radiogenic cancers, Health Physics 95 (1) (2008) 119–147. doi:10.1097/01.HP.0000291191.49583.f7.

[14] P. Coenen, S. Kezic, D. J. J. Heederik, S. Peters, H. F. v. d. Molen, Applying a 'presumably plausible' principle in a new one-time financial compensation system for occupational diseases in the netherlands, Occupational and Environmental Medicine 81 (10) (2024) 529–531. doi:10.1136/oemed-2024-109533.

[15] H. Kromhout, D. J. J. Heederik, Using job exposure matrices to estimate an individual's exposure for compensation?, Occupational and Environmental Medicine 83 (1) (2026) 58–60. doi:10.1136/oemed-2025-110290.

[16] J. Mancilla Galindo, M. Oude Voshaar, L. Portengen, D. van Klaveren, R. Vermeulen, S. Peters, Evaluation of the probability of causation for lung cancer workers' compensation: Scoping review protocol, Open Science Framework, published 5 June 2025 (2025). doi:10.17605/OSF.IO/9EVSY. URL https://osf.io/9evsy/

[17] D. Pieper, L. Puljak, Language restrictions in systematic reviews should not be imposed in the search strategy but in the eligibility criteria if necessary, Journal of Clinical Epidemiology 132 (2021) 146–147. doi:10.1016/j.jclinepi.2020.12.027.

[18] K. Hair, Z. Bahor, M. Macleod, J. Liao, E. S. Sena, The automated systematic search deduplicator (asysd): a rapid, open-source, interoperable tool to remove duplicate citations in biomedical systematic reviews, BMC Biology 21 (1) (2023) 189. doi:10.1186/s12915-023-01686-z.

[19] J. De Bruin, P. Lombaers, C. Kaandorp, J. Teijema, T. Van Der Kuil, B. Yazan, A. Dong, R. Van De Schoot, Asreview lab v.2: Open-source text screening with multiple agents and a crowd of experts, Patterns 6 (7) (2025) 101318. doi:10.1016/j.patter.2025.101318.

[20] J. Boetje, R. Van De Schoot, The safe procedure: a practical stopping heuristic for active learning-based screening in systematic reviews and meta-analyses, Systematic Reviews 13 (1) (2024) 81. doi:10.1186/s13643-024-02502-7.

[21] E.-A. Kim, E. Lee, S.-K. Kang, M. Jeong, Probability of causation for occupational cancer after exposure to ionizing radiation, Annals of Occupational and Environmental Medicine 30 (1) (2018) 3. doi:10.1186/s40557-018-0220-5.

[22] J. Djounova, N. Chobanova, I. Guleva, A. Milchev, I. Peyankov, K. Negoicheva, D. Panova, Health monitoring of npp workers, International Journal of Low Radiation 9 (4) (2014) 274. doi:10.1504/IJLR.2014.063411.

[23] A. Ulanowski, E. Shemiakina, D. Güthlin, J. Becker, D. Preston, A. I. Apostoaei, F. O. Hoffman, P. Jacob, J. C. Kaiser, M. Eidemüller, Prozes: the methodology and software tool for assessment of assigned share of radiation in probability of cancer occurrence, Radiation and Environmental Biophysics 59 (4) (2020) 601–629. doi:10.1007/s00411-020-00866-7.

[24] B. Armstrong, G. Thériault, Compensating lung cancer patients occupationally exposed to coal tar pitch volatiles., Occupational and Environmental Medicine 53 (3) (1996) 160–167. doi:10.1136/oem.53.3.160.

[25] D. Chmelevsky, D. Barclay, A. M. Kellerer, L. Tomasek, E. Kunz, V. Placek, Probability of causation for lung cancer after exposure to radon progeny: A comparison of models and data, Health Physics 67 (1) (1994) 15–23. doi:10.1097/00004032-199407000-00002.

[26] C. Land, Do gamma rays and alpha particles cause different types of lung cancer? a comparison between atomic bomb survivors and uranium miners, Radiation Protection Dosimetry 60 (4) (1995) 279–285. doi:10.1093/oxfordjournals.rpd.a082729.

[27] T. L. Guidotti, Apportionment in Asbestos-Related Disease for Purposes of Compensation., Industrial Health 40 (4) (2002) 295–311. doi:10.2486/indhealth.40.295.

[28] W. Jacobi, Radiation exposure and attributable cancer risk in former miners of the WISMUT uranium mining company, Kerntechnik 64 (1-2) (1999) 39–43. doi:10.1515/kern-1999-641-214.

[29] Z. Sun, Q. Liu, W. Tu, Q. Wang, J. Wang, Y. Wang, L. Du, C. Xu, J. Wang, [Dissection of GBZ 97-2017 Judgment standard for occupational radiogenic neoplasms: A computer software for occupational radiogenic neoplasm judgment] [chinese], International Journal of Radiation Medicine and Nuclear Medicine 43 (3) (2019) 285–290. doi:10.3760/cma.j.issn.1673-4114.2019.03.015.

[30] F. A. Cucinotta, Space Radiation Risks for Astronauts on Multiple International Space Station Missions, PLoS ONE 9 (4) (2014) e96099. doi:10.1371/journal.pone.0096099.

[31] D. P. Bhatia, M. S. S. Murthy, Probability of Causation For Radiation at Tributable Cancer in the Indian Population:, Health Physics 63 (4) (1992) 402–409. doi:10.1097/00004032-199210000-00004.

[32] M. Ichikawa, T. Iwasaki, S. Kobayashi, H. Matsudaira, [application of NIH radioepidemiological tables to Japanese population] [japanese], Japanese Journal of Health Physics 23 (2) (1988) 131–140. doi:10.5453/jhps.23.131.

[33] J. Mancilla-Galindo, S. Peters, H. Deng, H. F. Van Der Molen, H. Kromhout, L. Portengen, R. Vermeulen, D. Heederik, Probability of causation in individual workers: Lung cancer due to occupational exposure to asbestos (Feb. 2026). doi:10.64898/2026.02.06.26345596.

[34] F. Hérin, F. Savall, P. Saint-Martin, N. Telmon, [Compensation of damage in cancerology] [french], Bulletin du Cancer 108 (4) (2021) 352–358. doi:10.1016/j.bulcar.2020.11.021.

[35] M. B. Lax, R. Klein, More than meets the eye: Social, economic, and emotional impacts of work-related injury and illness, NEW SOLUTIONS: A Journal of Environmental and Occupational Health Policy 18 (3) (2008) 343–360. doi:10.2190/NS.18.3.i.

[36] C. Looker, H. Kelly, No-fault compensation following adverse events attributed to vaccination: a review of international programmes, Bulletin of the World Health Organization 89 (5) (2011) 371–378. doi:10.2471/BLT.10.081901.

[37] H. Whiteman, Workers' compensation and catastrophic injuries, Topics in Spinal Cord Injury Rehabilitation 6 (4) (2001) 13–19. doi:10.1310/L1HY-NTQ5-XHLU-WWWU.

[38] J. Robins, S. Greenland, Estimability and estimation of expected years of life lost due to a hazardous exposure, Statistics in Medicine 10 (1) (1991) 79–93. doi:10.1002/sim.4780100113.

[39] M. Eidemüller, J. Becker, J. C. Kaiser, A. Ulanowski, A. I. Apostoaei, F. O. Hoffman, Concepts of association between cancer and ionising radiation: accounting for specific biological mechanisms, Radiation and Environmental Biophysics 62 (1) (2023) 1–15. doi:10.1007/s00411-022-01012-1.

[40] K. Silver, B. Wilson, The Energy Employees Occupational Illness Compensation Program Act, Federal Facilities Environmental Journal 16 (3) (2005) 89–104. doi:10.1002/ffej.20065.

[41] K. Lippel, [Recognition of occupational cancers in Quebec] [french], in: Développements récents en droit de la santé et de la sécurité du travail, Vol 394, Éditions Yvon Blais, Cowansville, QC, 2015, pp. 297–368. doi:10.2139/ssrn.3585403.

[42] G. Caravagna, A. Graudenzi, D. Ramazzotti, R. Sanz-Pamplona, L. De Sano, G. Mauri, V. Moreno, M. Antoniotti, B. Mishra, Algorithmic methods to infer the evolutionary trajectories in cancer progression, Proceedings of the National Academy of Sciences 113 (28) (Jul 2016). doi:10.1073/pnas.1520213113.

[43] A. P. Dawid, M. Musio, R. Murtas, The probability of causation, Law, Probability and Risk 16 (4) (2017) 163–179. doi:10.1093/lpr/mgx012.

[44] D. Loomis, N. Guha, A. L. Hall, K. Straif, Identifying occupational carcinogens: an update from the iarc monographs, Occupational and Environmental Medicine 75 (8) (2018) 593–603. doi:10.1136/oemed-2017-104944.

[45] International Agency for Research on Cancer, List of classifications by cancer sites with sufficient or limited evidence in humans, IARC monographs volumes 1–141 (2026).
URL https://monographs.iarc.who.int/agents-classified-by-the-iarc

[46] M. Borenstein, J. P. T. Higgins, L. V. Hedges, H. R. Rothstein, Basics of meta-analysis: $I^2$ is not an absolute measure of heterogeneity, Research Synthesis Methods 8 (1) (2017) 5–18. doi:10.1002/jrsm.1230.

[47] M. Klose, P. N. Zivich, S. R. Cole, Revisiting the population attributable fraction, Epidemiology 36 (4) (2025) 482–486. doi:10.1097/EDE.0000000000001867.

[48] M. Von Cube, M. Schumacher, S. Bailly, J. Timsit, A. Lepape, A. Savey, A. Machut, M. Wolkewitz, The population-attributable fraction for time-dependent exposures and competing risks—a discussion on estimands, Statistics in Medicine 38 (20) (2019) 3880–3895. doi:10.1002/sim.8208.

[49] F. A. Cucinotta, L. J. Chappell, M.-H. Y. Kim, M. Wang, Radiation Carcinogenesis Risk Assessments for Never-smokers, Health Physics 103 (5) (2012) 643–651. doi:10.1097/HP.0b013e318267b3ad.

[50] C. E. Grueber, S. Nakagawa, R. J. Laws, I. G. Jamieson, Multimodel inference in ecology and evolution: challenges and solutions, Journal of Evolutionary Biology 24 (4) (2011) 699–711. doi:10.1111/j.1420-9101.2010.02210.x.

[51] A. Stabilini, L. Hafner, L. Walsh, Comparison and multi-model inference of excess risks models for radiation-related solid cancer, Radiation and Environmental Biophysics 62 (1) (2023) 17–34. doi:10.1007/s00411-022-01013-0.

[52] X. A. Harrison, L. Donaldson, M. E. Correa-Cano, J. Evans, D. N. Fisher, C. E. Goodwin, B. S. Robinson, D. J. Hodgson, R. Inger, A brief introduction to mixed effects modelling and multi-model inference in ecology, PeerJ 6 (2018) e4794. doi:10.7717/peerj.4794.

[53] F. Zhou, K. He, Y. Ni, Tree-based additive noise directed acyclic graphical models for nonlinear causal discovery with interactions, Biometrics 81 (3) (07 2025). doi:10.1093/biomtc/ujaf089.

[54] A. Olsson, L. Bouaoun, J. Schüz, R. Vermeulen, T. Behrens, C. Ge, H. Kromhout, J. Siemiatycki, P. Gustavsson, P. Boffetta, et al., Lung cancer risks associated with occupational exposure to pairs of five lung carcinogens: Results from a pooled analysis of case-control studies (synergy), Environmental Health Perspectives 132 (1) (2024) 017005. doi:10.1289/EHP13380.

[55] M. Rubinstein, M. Cuellar, D. Malinsky, Mediated probabilities of causation, Journal of Causal Inference 13 (1) (2025) 20240019. doi:10.1515/jci-2024-0019.

[56] R. Diaz-Uriarte, I. G. Johnston, A picture guide to cancer progression and evolutionary accumulation models: Systematic critique, plausible interpretations, and alternative uses, IEEE Access 13 (2025) 62306–62340. doi:10.1109/ACCESS.2025.3558392.

[57] A. Zeka, R. Gore, D. Kriebel, The two-stage clonal expansion model in occupational cancer epidemiology: results from three cohort studies, Occupational and Environmental Medicine 68 (8) (2011) 618–624. doi:10.1136/oem.2009.053983.

[58] D. B. Richardson, Lung cancer in chrysotile asbestos workers: analyses based on the two-stage clonal expansion model, Cancer Causes & Control 20 (6) (2009) 917–923. doi:10.1007/s10552-009-9297-z.

[59] J. Robins, S. Greenland, The probability of causation under a stochastic model for individual risk, Biometrics 45 (4) (1989) 1125. doi:10.2307/2531765.

[60] C. C. Maas, D. Van Klaveren, O. Visser, M. A. Merkx, H. F. Lingsma, V. E. Lemmens, A. G. Dinmohamed, Number of life-years lost at the time of diagnosis and several years post-diagnosis in patients with solid malignancies: a population-based study in the netherlands, 1989–2019, eClinicalMedicine 60 (2023) 101994. doi:10.1016/j.eclinm.2023.101994.