ORIGINAL PAPER

Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

WILEY

E-synthesis for carcinogenicity assessments: A case study of processed meat

Francesco De Pretis PhD[1] | Saana Jukola PhD[2,3] | Jürgen Landes PhD[4,5]

[1]Department of Communication and Economics, University of Modena and Reggio Emilia, Reggio, Emilia, Italy

[2]Department of Philosophy I, Ruhr-University Bochum, Bochum, Germany

[3]Institute for Medical Humanities, University Clinic Bonn, University of Bonn, Bonn, Germany

[4]Munich Center for Mathematical Philosophy, Faculty of Philosophy, Philosophy of Science and Study of Religion, Ludwig-Maximilians-Universität München, München, Germany

[5]Open Science Center, Ludwig-Maximilians-Universität München, München, Germany

Correspondence
Jürgen Landes, PhD, Munich Center for Mathematical Philosophy, Faculty of Philosophy, Philosophy of Science and Study of Religion, Ludwig-Maximilians-Universität München, 80539 München, Germany.
Email: juergen_landes@yahoo.de

Abstract

Rationale, Aims and Objectives: Recent controversies about dietary advice concerning meat demonstrate that aggregating the available evidence to assess a putative causal link between food and cancer is a challenging enterprise.

Methods: We show how a tool developed for assessing putative causal links between drugs and adverse drug reactions, E-Synthesis, can be applied for food carcinogenicity assessments. The application is demonstrated on the putative causal relationship between processed meat consumption and cancer.

Results: The output of the assessment is a Bayesian probability that processed meat consumption causes cancer. This Bayesian probability is calculated from a Bayesian network model, which incorporates a representation of Bradford Hill's Guidelines as probabilistic indicators of causality. We show how to determine probabilities of indicators of causality for food carcinogenicity assessments based on assessments of the International Agency for Research on Cancer.

Conclusions: We find that E-Synthesis is a tool well-suited for food carcinogenicity assessments, as it enables a graphical representation of lines and weights of evidence, offers the possibility to make a great number of judgements explicit and transparent, outputs a probability of causality suitable for decision making and is flexible to aggregate different kinds of evidence.

KEYWORDS
Bayesian network, cancer, causality, E-synthesis, evidence aggregation, meat

1 | INTRODUCTION

The number of studies investigating relationships between particular foods and particular aspects of cancer and its onset, prediction, prevention and treatment is growing at a rapid and increasing pace. However, growing bodies of evidence do not always produce consensus. For example, the possible causal relationship between the consumption of meat products and cancer is currently fiercely debated.[1–7]

Underlying this dispute is a disagreement on how to assess and amalgamate the available evidence.[6] One side of the dispute insists on giving priority to well-conducted randomized controlled trials (RCTs) in drawing causal inferences from data.[5,7–9] This side of the dispute denies that there is decisive evidence for a causal relationship if there are no RCTs showing a causal relationship. The other side of the debate maintains the sufficiency of observational studies and/or points to methodological deficiencies of RCTs investigating causal

relationships between nutrition and cancer.[10–13] For example, observational studies are often much cheaper to conduct[14] and hence record many more person years,[15] and it is practically impossible to blind participants in RCTs on nutrition. Summing up, there is a dispute between evidence purists relying only on evidence of the prima facie highest quality[16] and evidence pragmatists taking what in philosophy of science has been referred to as total evidence approach.[17]

The challenge arises for those taking a total evidence approach to aggregate evidence from different study methodologies into a final useful assessment. In particular, possible confounding and biases in observational studies should be modelled and then the thusly modelled evidence needs to be amalgamated with available RCTs. Even though there are some suggestions for strength of evidence assessment tools that take into consideration contributions of diverse methods,[12] the aggregation of assessments of evidence originating from different study types (RCTs, observational studies and basic science studies) is often hard to carry out quantitatively[18] and the final aggregation of assessments is then based on a narrative review. These reviews necessarily rely on a number of implicit and intransparent judgements that make the final assessment somewhat opaque.[19] Furthermore, the final assessment is often communicated in a form that is not ready-to-use in concrete decision problems, for example, a probability that a certain action will lead to a desired outcome.

E-Synthesis is an emerging tool for drug safety assessments,[20–25] modelling confounding and biases of observational studies and RCTs. It offers a principled approach to produce a posterior probability of causal relationships given evidence produced by diverse observational and randomized studies. In this study, we consider its applicability as a tool for food carcinogenicity assessments exemplified by an application to the disputed causal relationship between processed meat and cancer. E-Synthesis can address the above mentioned challenges for aggregating bodies of evidence on food carcinogenicity, as it (1) seamlessly aggregates evidence from different methodologies (randomized studies, observational studies and mechanistic evidence), (2) it outputs a Bayesian probability[26] that a food causes an adverse health effect in a population of food consumers that is ready-to-use for decision making and (3) it makes a number of judgements explicit and open to inspection and criticism that may remain opaque otherwise.

2 | MATERIALS AND METHODS

We now show how E-Synthesis[20–25] can be employed as a tool for food carcinogenicity assessment, see also the Appendix (A Primer on Bayesian Reasoning).

2.1 | Theoretical constructs

A causal hypothesis linking a particular food or substance to (a particular) cancer in a population consuming this food or substance is the starting point. As such causal relationships cannot be observed directly, the framework incorporates indicators of causality, which are

observable consequences of the causal hypothesis of interest. Learning that a nonempty subset of indicators of causality likely hold increases the probability that the causal hypothesis is true. Learning that a nonempty subset of indicators of causality likely fails to hold decreases the probability that the causal hypothesis is true. Absence of evidence does not lead to a change of probabilities. We here consider the causal hypothesis that processed meat consumption causes cancer.

The indicators of causality are based on best practice medical inference modelling Bradford Hill Guidelines, cf. Table 1.[27] The International Agency for Research on Cancer (IARC) also employs these guidelines.[28] The indicators are as follows: (1) probabilistic dependence, (2) dose–response relationship, (3) rate of growth, (4) mechanism, (5) temporality and (6) difference making. The indicators are true, respectively, if (1) there exists a positive correlation between processed meat consumption and cancer, (2) there is a clear DR between processed meat consumption and cancer, (3) the DR is strongly increasing, (4) there is a 'linkage between a direct molecular initiating event […] and an adverse outcome at a biological level of organization relevant to risk assessment',[29] (5) processed meat consumption precedes cancer on the relevant time scale and (6) there exists a counterfactual difference between processed meat consumption and cancer. In principle, E-Synthesis is flexible to incorporate a set of different indicators of causality.

Evidence is then informative about subsets of indicators. For example, randomized studies in human populations are informative about difference making, observational studies of human populations can be informative about probabilistic dependence, dose–response relationship, rate of growth and temporality. Basic science studies inform us about the causality indicator called mechanism.

Evidential modulators apply to the studies to track the methodology and qualities of studies. Concerning internal validity, observational studies of human populations are modulated by their power (sample size), the time studied (duration), their covariate

TABLE 1 Mapping of Bradford Hill Guidelines into the E-Synthesis framework according to Figure 2[21]

Bradford Hill Guidelines	Roles within E-Synthesis
Strength of association	Rate of growth, dose–response and probabilistic dependence
Consistency	*Inferential patterns*
Specificity	Difference making
Temporality	Temporality
Biological gradient	Rate of growth, dose–response and probabilistic dependence
Plausibility	Mechanistic knowledge and *inferential patterns*
Coherence	*Inferential patterns*
Experiment	Difference making and *empirical level/ methodology*
Analogy	Relevance and *empirical level/methodology*

Note: Italics here represent 'dimensions of scientific research'.

754 | WILEY— Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

TABLE 2 Assessed studies, the indicators they pertain to, assessed modulators and conditional probabilities

No.	Study	Indicator	ES	SB	A	SS	$P(ES\mid Ind)$	$P(ES\mid \overline{Ind})$
1	Rosato et al.[80]	PD	1	0	0	0.6	0.650	0.350
2	Shayanfar et al.[81]	PD	0	0	0	0.2	0.450	0.550
3	Um et al.[82]	PD	1	0	0	0.4	0.600	0.400
4	Yin and Bostick[83]	PD	1	0	0	0.4	0.600	0.400
5	Pournaghi et al.[38]	RoG	1	0	1	0.1	0.775	0.225
6	Fereidani et al.[84]	PD	1	0	0	0.2	0.550	0.450
7	Ziouziou et al.[85]	RoG	1	0	0	1	0.750	0.250
8	Ziouziou et al.[86]	RoG	1	0	0	1	0.750	0.250

Note: We employed the mentioned simplification to binary variables with values 0 and 1. Here, 1 stands for a positive value, for example, the presence of sponsorship bias, and 0 stands for absence of sponsorship bias. The values specified in the table represent our assessments.

Abbreviations: A, adjustment and stratification; ES, effect size; *Ind*, indicator of causality; P, probability function; PD, probabilistic dependence; *RoG*, rate of growth; *SS*, sample size.

TABLE 3 Posterior probability of © (hypothesis of causality) with accumulating evidence for different initial priors (from 1% to 10%)

Study	Prior probability of ©		
	0.1	0.05	0.01
Rosato et al.[80]	0.163	0.084	0.017
Shayanfar et al.[81]	0.140	0.072	0.015
Um et al.[82]	0.189	0.099	0.021
Yin and Bostick[83]	0.245	0.133	0.029
Pournaghi et al.[38]	0.404	0.243	0.058
Fereidani et al.[84]	0.441	0.272	0.067
Ziouziou et al.[85]	0.643	0.460	0.141
Ziouziou et al.[86]	0.800	0.654	0.266
Posterior probability of ©	0.800	0.654	0.266

Note: Every row indicates the probability of © given the body of evidence up to and including this row. Calculations are based on the Bayesian network formalism presented in Section 3; the conditional probabilities of the evidence are given in Table 2, and the graph of the Bayesian network (without modulator variables) is shown in Figure 2.

Abbreviation: ©, causal hypothesis of interest.

analysis (adjustment and stratification) and the assessed conflicts of interest (sponsorship bias). Randomized studies of human populations are also modulated by what sets them apart from observational studies (blinding, randomization and placebo control). External validity is modulated by the degree to which the studied population is relevant (in terms of relevant similarities) to the target population.

These modulators influence how much the available evidence changes the plausibility of indicators of causality. For example, a poorly designed observational study reporting a rather weak dose–response relationship may only marginally increase our belief in the existence of an actual DR between processed meat and cancer. Since the existence of a dose–response relationship can also be due to confounding, our belief in the truth of the causal hypothesis increases even less.

2.2 | Bayesian network approach

This three-layered structure consisting of the causal hypothesis (Layer 1), testable consequences (Layer 2) and the evidence and its modulators (Layer 3) is an instance of a "Hierarchy-of-Hypotheses" approach.[30] A blueprint for creating Bayesian networks to compute a probability of the causal hypothesis in Layer 1 given modulated evidence (Layer 3) has been provided.[31] E-Synthesis implements and modifies this blueprint providing a Bayesian network that allows one to calculate the probability of the causal hypothesis of interest given an available modulated body of evidence. An overview of the most important notation and abbreviations can be found in Table 4.

Bayesian networks are a popular tool for reasoning with and representing probabilities defined over a finite set of variables.[32] The variables together with a set of directed arrows between pairs of variables form a directed acyclic graph. The graph is called directed due to the arrows having a direction. Acyclicity means that directed cycles are not permitted; it is hence impossible to walk along the arrows and return to the starting point. The set of directed arrows encodes probabilistic independence relations. To specify a probability function consistent with these independence relations, one first determines for every variable X the set of its parent variables $\vec{Y}$. A variable Y is called a parent of X, if and only if there exists a directed edge originating at the parent variable Y pointing to said variable X. Secondly, for all truth values of all variables X and all truths values of the respective set of parents, one chooses a probability between 0 and 1. These choices have to sum to 1 in an appropriate sense, for every fixed variable X and fixed truth values of all its parent variables $\vec{Y} = \vec{y}$ the sum over the possible values of X has to equal 1:

$$\sum_x P(X = x \mid \vec{Y} = \vec{y}) = 1$$

2.3 | The generic model

Applying E-Synthesis, we then create one variable for the causal hypothesis of interest (©), one variable for every indicator of causality (PD, DR, RoG, M, T, Δ), one variable for every

TABLE 4 Notation and abbreviations

$\overline{V}$	Negation of binary variable V
P	Probability function
$P(\cdot|\cdot)$	Conditional probability function
©	Causal hypothesis of interest
Ind	Indicator of causality
PD	Probabilistic dependence, indicator of causality
DR	Dose–response relationship, indicator of causality
RoG	Rate of growth, indicator of causality
M	Mechanism, indicator of causality
T	Temporality, indicator of causality
Δ	Difference making, indicator of causality
A	Adjustment and stratification
SS	Sample size
ES	Effect size
REP	Report
$\&$	Conjunction symbol

study in the to be aggregated body of evidence and for every evidential variable a set of pertinent modulator variables is created.

Directed arrows are inserted as follows: there are six arrows originating from © pointing towards the six indicators of causality. If a study is informative about an indicator variable other than PD or DR, then there is an arrow originating from the indicator variable and pointing to the evidential variable. Furthermore, RoG is a parent of DR and DR a parent of PD. If the indicator variable is PD or DR, then the arrow is only inserted, if the study is not also informative about DR or RoG, respectively. Finally, the modulator variables are the parents of their respective evidential variables, see Figure 1 for a graphical representation.

Probabilities of the variables conditional on the set of parent variables are set as described above. The probabilities reflect one's knowledge and judgements based on the available background knowledge.

3 | RESULTS

We now exemplify how E-Synthesis can be a tool for food carcinogenicity assessments by considering a possible causal relationship between processed meat and cancer. Our focus is on showing how an application of this tool works in principle. We hence only consider a few select studies rather than a substantial body of evidence. Furthermore, we focus on how to set (conditional) probabilities in principle and are less interested in the concrete values.
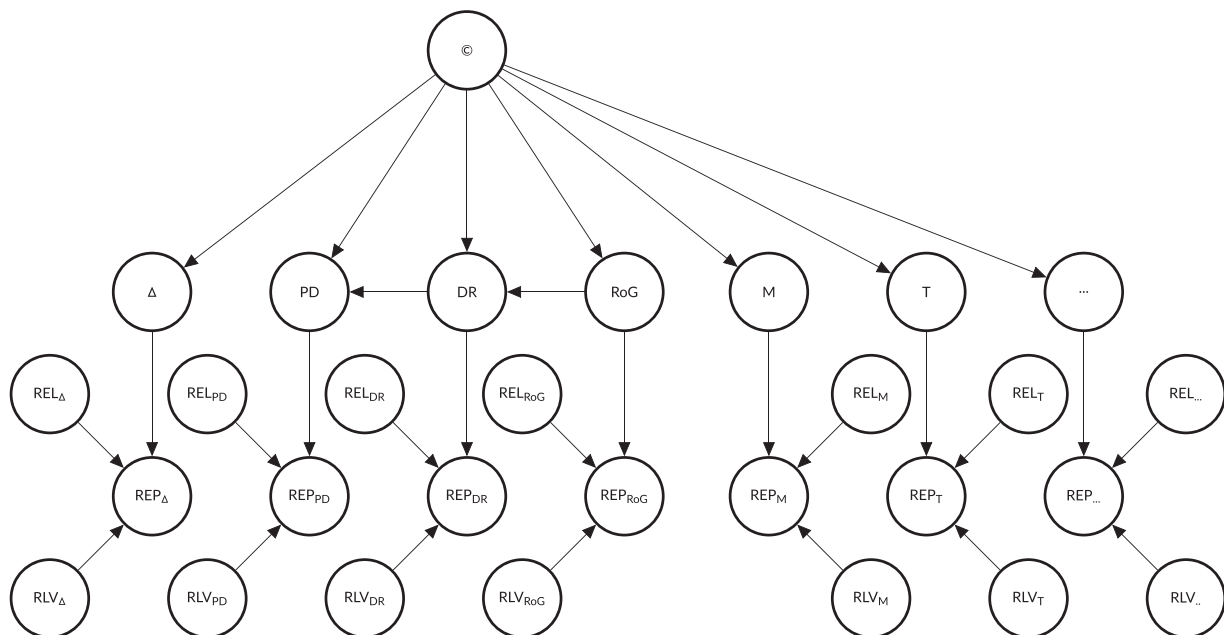

FIGURE 1 Graph of the Bayesian network with one report for every causal indicator variable given in Landes et al.[21] The dots indicate that there might be further indicators of causality. The nodes reliability (REL) and relevance (RLV) are evidential modulators variables of studies, REP nodes.

756 | WILEY— Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

3.1 | Conditional probabilities of causality and its indicators

The prior probability of processed meat consumption causing cancer is based only on the available background knowledge and not on the specific evidence on meat consumption and cancer to be aggregated. This prior probability, $P(©)$, is eventually updated by the available and modulated evidence to a posterior probability, $P(©|\mathcal{E})$ (read as: probability of causality given the evidence $\mathcal{E}$). For ease of presentation all variables used are binary (with the exception of sample size (SS). As the value of SS is known with certainty, SS is not much of a variable, cf. Section 3.4). A generalization to variables of greater arity is straightforward but cumbersome.

Some conditional probabilities of the indicators of causality follow from their relationships (with $©$). A strong dose–response relationship entails the existence of a dose–response relationship, which in turn entails a positive correlation. Furthermore, causality entails T and M. Following De Pretis et al.,[20] we equate Δ with $©$, as we are not interested in philosophical disputes on the nature of causality. We hence obtain the following conditional probabilities

$$P(DR|RoG) = 1 \quad P(PD|DR) = 1 \quad P(M|©) = 1$$
$$P(T|©) = 1 \qquad P(\Delta|©) = 1 \quad P(\Delta|\overline{©}) = 0.$$

Ontologically, the conditional probabilities of indicators of causality are best interpreted by natural frequencies, for example, the proportion of agents that cause cancer also do so in a strong dose–response relationship equals $P(RoG|©)$.

We extracted such frequencies from the IARC monographs for the remaining conditional probabilities of indicators of causality not covered by the above considerations, if $©$ is true. The conditional probabilities we thus determine are $P(RoG|©)$, $P(DR|\overline{RoG}\ \&©)$ and $P(PD|\overline{DR}\ \&\ \overline{RoG}\ \&©)$.

How strongly Class 1 agents satisfied all nine of Hill's guidelines has been assessed (see Tables A1 and A2).[33] To select a pertinent reference class for food carcinogenicity assessment, we firstly excluded all general occupational exposures (i.e., furniture and cabinet making), while including those with a selective definition (i.e., wood dust). Secondly, evidence of absence and absence of evidence for dose response were represented by the same number (Table A2).[33] For thusly assessed agents, we studied the respective most recent IARC monograph and assessed whether IARC reported that $RoG\ \&©$, $DR\ \&\ \overline{RoG}\ \&©$ or $PD\ \&\ \overline{DR}\ \&\ \overline{RoG}\ \&©$ holds (Table A3) or whether there still is absence of evidence (Table A4). Our more fine-grained assessments of these agents supersede the previous assessments.

The nonsuperseded assessments by Swaen and van Amelsvoort,[33] as well as our assessments of DR were translated into the conditional probabilities as follows. If this degree for an agent had been assessed to be 90% or greater, indicating a strong dose-response relationship, then we represented this as case of $RoG\ \&©$ being true. A degree between 50% and 90% is represented by $DR\ \&\ \overline{RoG}\ \&©$ and degree <50% is represented by $PD\ \&\ \overline{DR}\ \&\ \overline{RoG}\ \&©$. For all agents where the dose-

response relationship was assessed to be below 50%, a positive correlation between agent and cancer was assessed.

There are 68 agents relevant to our study, see Table A3. Thirty-two agents were assessed to be in the range 90–100 indicating RoG and 29 agents were in the range 50–90 indicating a modest (not strong) dose-response relationship $DR\ \&\ \overline{RoG}$ and 7 agents were in the range 0–50 indicating a lack of a dose-response relationship. We assessed that all agents in the range 0–50 were positively correlated to cancer $PD\ \&\ \overline{DR}\ \&\ \overline{RoG}\ \&©$.[1] So,

$$P(RoG|©) = \frac{32}{68} = \frac{8}{17} \approx 47\%$$
$$P(DR|\overline{RoG}\ \&©) = \frac{29}{68-32} = 80.\overline{5}\,\% \quad P(PD|\overline{DR}\ \&\ \overline{RoG}\ \&©) = 1.$$

Unfortunately, there is no suitable knowledge base from which we could extract the conditional probabilities for noncarcinogenic agents, that is, when $\overline{©}$ holds. We thus follow[20] and let

$$P(RoG|\overline{©}) = \frac{3}{700} \quad P(DR|\overline{RoG}\ \&\overline{©}) = \frac{18}{697}$$
$$P(PD|\overline{DR}\ \&\overline{©}) = \frac{4}{97}.$$

In case there is no causal relationship between an agent and cancer in reality, we are indifferent on the truth value of temporality. Furthermore, due to the great number possible ways that agent could potentially cause cancer, we follow[20] and adopt an indifference prior for $P(M|\overline{©}) = 0.5$.

3.2 | Temporality

The indicator of causality called temporality concerns information about relevant temporal aspects of cancer and processed meat consumption, for example, is processed meat consumed within the right time frame to cause cancer or is cancer the reason for a change in diet?[34,35]

3.3 | Choice of body of evidence

At the end of 2015, IARC classified processed meat as a Class 1 carcinogenic agent.[36] We wanted to assess primary evidence that has since then been produced. As we here restrict ourselves to exemplifying the application of E-Synthesis, we restricted our search to publications appearing in Nutrition and Cancer from January 2016 to December 2020.

On April 27, 2021, we searched that journal (search string: "processed meat") and found 62 studies published between 2016 and 2020 (including studies published ahead of print). E-Synthesis is

---

[1]In principle, causality does not necessarily entail a positive correlation, as the following somewhat contrived example shows. Smoking causes cancer and reduces the distance one can run. Running along dirty roads also causes cancer. Thus, smoking has some preventative effect (in this hypothetical[!] example). If the numbers are set in just the right way, then smoking causes cancer but also prevents cancer at the same rate. On the population level, there may hence be no positive correlation between smoking and cancer.

a methodology for evidence aggregation, we hence excluded all studies that are aggregations of previously published studies and all studies that did not report specifically on processed meat. Furthermore, we excluded all studies that did not report processed meat as a separate category and all studies with surrogate measures severing the direct link between processed meat and cancer (e.g., studies only investigating the relationship between processed meat and inflammatory indexes and/or inflammatory indexes and cancer). We also excluded all basic science and animal studies; how E-Synthesis can be employed to include such studies has been demonstrated.[20,22]

3.4 | Methodology of assessments

Nine studies satisfied all these constraints. We excluded one study reporting unclear results,[37] which could not sensibly be modelled by our binary outcome variable, $ES \in \{0, 1\}$ and $ES = 1$ meaning that a significant effect was found. The remaining eight studies are enumerated in Table 2, where we also report the indicators they pertain to, their assessed evidential modulators and the relevant conditional probabilities, see Equation (1).

auTo simplify matters, we did not distinguish between different types of processed meat (which are rarely reported in the primary studies) and the different types and locations of cancer (there were only few studies on the same type and location of cancer). Furthermore, we do not distinguish between different processed meat consuming populations. We hence made the simplifying assumption of a perfect external validity and omitted the relevance variables.

Sponsorship bias was always assessed as nonpresent, as no thor reported commercial sponsorship, $SB = 0$. Only one study stated adjustments for potential confounders.[38] More thorough assessments of these modulators are required for more realistic applications of

E-Synthesis. To represent the sample size, we used a logarithmic modelling through a geometric progression of the type $a_n = 2 \cdot a_{n-1} + 100$, with $a_0 = 0$. SS was set to 0 if the reported sample of patients in the study was less than a_1, whereas $SS = 1$ for $SS > 1,022,100$. In between, we discretized the variable SS with decimal step size.

None of the eight studies was assessed to be informative about T. All studies are observational. T and Δ hence do not have children in the Bayesian network (Figure 2).

E-Synthesis uses the follow-up time after drug use as a relevant modulator for assessing the (un-)safety of a drug. In that context, it is relevant for how long patients are followed up after treatment. The studies we assessed here were all of a different study design; these studies all reported dietary patterns of patients diagnosed with cancer and controls. The duration of these studies, the time period of collected data, is irrelevant in these studies, what matters is the sample size. We hence excluded the duration variable in De Pretis et al.,[20] D, from consideration. The formulae for conditional probabilities of observing a positive effect size given that the indicator holds, respectively, fails to hold, thus are

$$P(ES = 1|Ind) = 0.5 + \frac{A + SS}{4}$$
$$P(ES = 1|\overline{Ind}) = 0.5 - \frac{A + SS}{4}. \tag{1}$$

These simplistic formulae exemplify the working of E-Synthesis. More work is required to obtain formulae more suitable for real-world assessments.[39]

The resulting Bayesian network is shown in Figure 2. As this exemplification of E-Synthesis does not require the modelling of uncertainties of evidence modulator variables, there are no relevance and no reliability variables displayed in the graph. Furthermore, as we did not consider basic science studies and there were no randomized
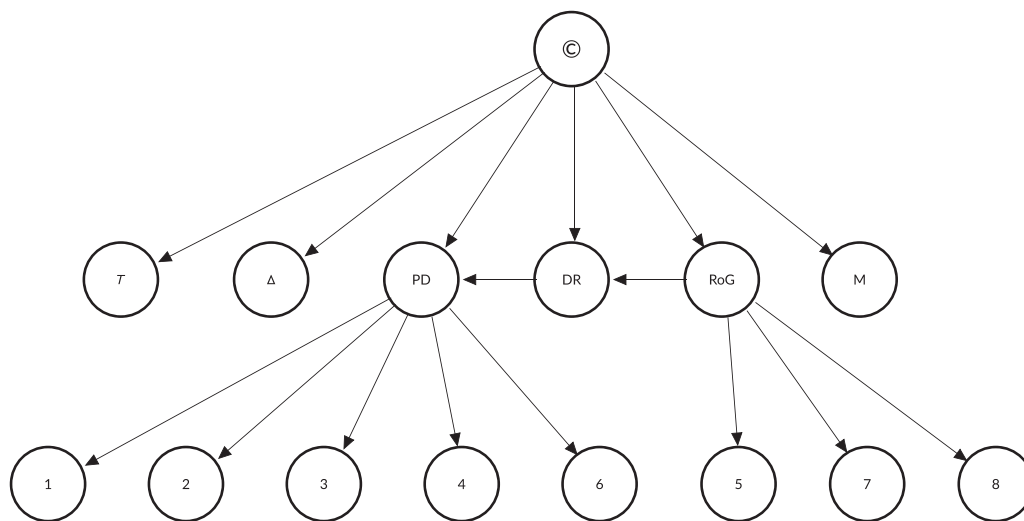

FIGURE 2 Directed acyclic graph of the Bayesian network used to compute the posterior probability of © (Hypothesis of Causality). The considered studies are reported according to their study number (see Table 2). Evidential modulator variables are not shown to simplify the exposition.
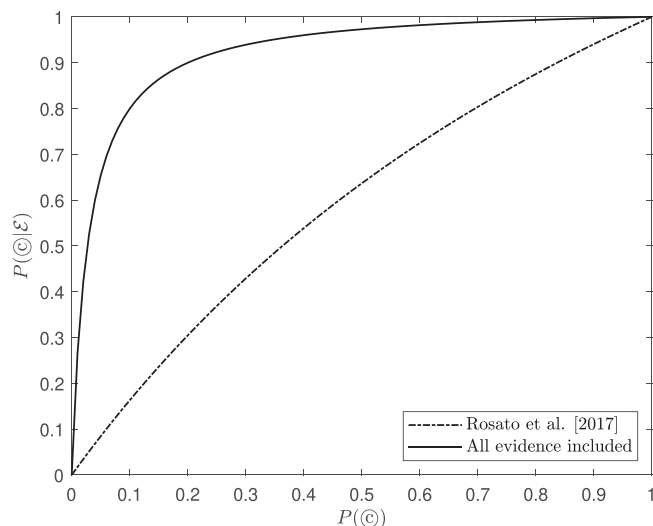
758 | **WILEY**— Journal of **Evaluation** in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

FIGURE 3 Posterior probability of the causal hypothesis © depending on the prior probability of ©. Solid curve shows the posterior given all the evidence, dotted curve shows posterior of taking only the first study into account.

studies in our body of evidence, the variables T, M and Δ do not have children.

3.5 | Aggregated evidence

We report the posterior probability of the causal hypothesis, $P(©|\mathcal{E})$, in Table 3 and Figure 3 depending on the prior probability, $P(©)$. We want to stress again that these values are obtained using simplistic formulae that have not been validated; Equation (1) and some conditional probabilities of indicators of causality still need significant further improvements.

These numbers display the dynamical behaviour of the posterior probability of ©. This probability increases with every study reporting some positive association between processed meat and cancer and decreases with the null result. Furthermore, Figure 3 displays the lack of randomized and basic science studies. All evidence we collected consisted of observational evidence at the population level.

4 | DISCUSSION

4.1 | Comparing food safety assessments to drug safety assessments

Food and drug safety assessments share a number of common properties, which facilitate the repurposing of methodology. Firstly, RCTs normally fail to reach required numbers of patient months to reliably secure causal inferences.[6,11,40–43] They fail for drug safety assessments, because they do not last long enough (adverse drug reactions may manifest only after a long time (years of treatment with olanzapine cause tardive dyskinesia,[44] treatment of pregnant women with diethylstilbestrol (DES) caused vaginal adenocarcinoma in their pubertal and adult children[45]) and they study too few patients[15] (serious adverse reactions may be very rare but so severe that the risk-benefit balance becomes negative in some cases, 1 fatality in every 10,000 patients[46]).

The (un-)safety of food stuffs and drugs depends on a greater number of concomitant factors including genetics, overall health and diet. Consuming moderated amounts of salted chips is, presumably, fine with a otherwise low salt diet but not with an otherwise high-salt diet. Drugs and their metabolites are also affected by our diet, even food stuffs that are apparently innocuous can cause major disruptions to the proper functioning of drugs, for example, the consumption of grapefruit juice is now known to have enabled fatal adverse drug reactions.[47]

Food and drugs are big business inducing significant incentives acting on market participants and evidence producers. Evidence is subsequently regularly biased.[48–51] For instance, in drug research there have been cases of industry funded RCTs in which study outcomes have been chosen in a way that makes detecting adverse effects less likely.[52] Similarly, the food and beverage industry has been linked to RCTs designed not to be able to detect negative effects of dietary choices.[53] Evidence assessors and policymakers need to consider potential biases, including their own biases, at all times.

The need to assess and incorporate assessed biases in evidence aggregation procedures as well as hard questions about causal inference from data have contributed to the development of lively debates on (the) appropriate standards of evidence for safety assessments. Both in the context of assessing drug safety and in research to adverse health effects of food stuffs or dietary choices, it has been argued that RCTs may not be as strong as when drug efficacy claims are evaluated.[6,54] Consequently, in both fields evidence assessment and aggregation methods alternative to GRADE and other tools placing the results from RCTs above other study types have been called for.[54–58]

There are also some dissimilarities to note. Firstly, plants and animals normally vary by location and season entailing that the nutritional value, chemical composition and so on of our food slightly varies in time and location. Virtually, all properly factory-produced drugs do not significantly vary.

In the European Union, nonrandomized studies are given explicit weight when it comes to drug safety assessments. The European Medicines Agency emphasizes the value of nonrandomized studies[59] and called for efforts to amalgamate safety signals such as spontaneous case reports, data-mining, pharmacoepidemiological studies, drug utilization studies and nonclinical studies.[19] The regulation of food safety assessments in the EU has yet to explicitly value evidence from nonrandomized evidence. The current regulation is noncommittal when it comes to evidence standards stating that assessments "shall be based on the available scientific evidence and undertaken in an independent, objective and transparent manner" (Regulation (EC) No 178/2002 §6.2).

4.2 | E-synthesis

The similarities between food and drug safety assessments make cross fertilization between the fields a priori plausible. Given the need to aggregate all the available evidence we chose to investigate the applicability of an E-Synthesis approach to food safety assessments. We exemplified an application of E-Synthesis on the suspected causal relationship between processed meat consumption and cancer. We gave a graphical summary of the lines of evidence (see Figure 2), made a number of judgements explicit and finally obtained a posterior probability of causality, which is suitable for decision making.

Although, E-Synthesis has been originally developed for drug safety assessment, it is more appropriate for food carcinogenicity assessments in two respects. Firstly, no proposal has been made to incorporate case reports in E-Synthesis. Although assessments of long- and short-term use of drugs are often based on case reports,[57,60,61] assessments of adverse health outcomes due to long term food consumption are normally not based on case reports. So, E-Synthesis is better suited for typical food carcinogenicity assessments than for typical drug safety assessments. Secondly, the freely available IARC monographs permit us to calculate conditional probabilities of indicators of causality. Drug-licensing agencies carrying out drug safety assessments do not publish documents listing all the evidence they base their assessments on.[62] Determining appropriate conditional probabilities is hence much harder in drug safety assessments.

Challenges and controversies can arise in applications of E-Synthesis when it comes to determining (conditional) probabilities. These probabilities represent assessments, for example, assessments of the degrees of sponsorship bias and blinding, as well as quality of covariate analysis. Assessments carried out by different actors are, in general, resulting in different probabilities. Differences between neutral researchers and experts working on behalf of food producers are bound to increase due to significant differences in their respective incentives. In our opinion, it would be wrong to blame these differences on the methodology used for safety assessments, as the methodology can only be as good as the assessments it uses as inputs. E-Synthesis at least makes such assessments transparent and open to scrutiny and debate. Furthermore, such assessments can be treated as parameters enabling robustness analyses studying the (in-)dependence of the posterior probability of © with respect to these parameters.

We hence find that E-Synthesis can serve as a well-motivated methodology for food carcinogenicity assessments.

4.3 | The meat and cancer debate

A series of articles published in the Annals of Internal Medicine in October 2019 reviewed evidence on the association between red and processed meat consumption and all-cause mortality, cardiometabolic outcomes and cancer.[2–6] The authors used systematic review methodology and the GRADE tool to assess the certainty of the evidence for the outcomes. The reviews concluded that the association between red and processed meat consumption and negative health outcomes is very small and the existing evidence is of low or very low certainty. In addition, the group of researchers published guidelines recommending that given the uncertainty of the existing evidence, adults can continue their red and processed meat consumption.[7] The publication of these articles raised a storm of critical responses and counter responses.[6,9,13]

Our approach fits into this debate as a contribution providing a methodology for aggregating evidence from randomized and non-randomized studies. Both sides of this debate may, in principle, use our approach. Their respective views on the weight of observational evidence is then reflected in different weights of the indicators of causality informed by observational evidence (conditional probabilities such as $P(PDI©)$ and $P(DRI©)$). The ferocity of this debate makes it rather unlikely that both sides can agree on conditional probabilities. Our approach of determining (some of) these probabilities in an objective manner from a database of known carcinogenic agents may be a methodological approach both sides might be willing to pursue.

4.4 | Related work and the wider context

To conclude the study, we briefly mention relevant related works situating our approach in a wider context.

Bayesian networks continue to be a popular tool for artificial intelligence (applications) and evidence aggregation tasks. Their versatility has facilitated academic studies on nutrition and health,[63,64] as well as food safety[65,66] and patents for predicting responses to food (US patent).

The methodology for risk and safety assessments is continuously developing. There is a fruitful back-and-forth between regulators[56,67] and academia,[62,68,69] as well as a growing number of proposals.[70–74] A particular focus lies on the role of real-world evidence (evidence obtained without randomization).[75] With the passing of the 21st Century Cures Act in the United States, real-world evidence may now also be used to argue for the efficacy of drugs. It seems unwise to assume that these methodological debates will soon be resolved.

Foundational aspects of these topics make contact with ethics,[76] the notion of healthy food,[77] cancer aetiology[1] and causal inference causal inference in health sciences.[21,78,79]

760 | WILEY—Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

ORCID

Francesco De Pretis [iD] http://orcid.org/0000-0001-8395-7833
Saana Jukola [iD] http://orcid.org/0000-0001-9740-309X
Jürgen Landes [iD] http://orcid.org/0000-0003-3105-6624

REFERENCES

1. Campbell TC. Nutrition and cancer: an historical perspective—the past, present, and future of nutrition and cancer. Part 2. Misunderstanding and ignoring nutrition. *Nutr Cancer*. 2017;69(6):962-968. doi:10.1080/01635581.2017.1339094
2. Han MA, Zeraatkar D, Guyatt GH, et al. Reduction of red and processed meat intake and cancer mortality and incidence. *Ann Intern Med*. 2019;171(10):711-720. doi:10.7326/M19-0699
3. Vernooij RW, Zeraatkar D, Han MA, et al. Patterns of red and processed meat consumption and risk for cardiometabolic and cancer outcomes. *Ann Intern Med*. 2019;171(10):732-741. doi:10.7326/m19-1583
4. Zeraatkar D, Han MA, Guyatt GH, et al. Red and processed meat consumption and risk for all-cause mortality and cardiometabolic outcomes. *Ann Intern Med*. 2019;171(10):703-710. doi:10.7326/m19-0655
5. Zeraatkar D, Johnston BC, Bartoszko J, et al. Effect of lower versus higher red meat intake on cardiometabolic and cancer outcomes. *Ann Intern Med*. 2019;171(10):721-731. doi:10.7326/m19-0622
6. Neuhouser ML.Red and processed meat: More with less? *Am J Clin Nutr*. 2019;111(2):252-255. doi:10.1093/ajcn/nqz294
7. Johnston BC, Zeraatkar D, Han MA, et al. Unprocessed red meat and processed meat consumption: Dietary guideline recommendations from the nutritional recommendations (NutriRECS) consortium. *Ann Intern Med*. 2019;171(10):756-764. doi:10.7326/m19-1621
8. Ioannidis JP. We need more randomized trials in nutrition—preferably large, long-term, and with negative results. *Am J Clin Nutr*. 2016;103(6):1385-1386. doi:10.3945/ajcn.116.136085
9. Ioannidis JPA. Neglecting major health problems and broadcasting minor, uncertain issues in lifestyle science. *JAMA*. 2019;322(21):2069-2070. doi:10.1001/jama.2019.17576
10. Jukola S. On the evidentiary standards for nutrition advice. *Stud Hist Philos Biol Biomed Sci STUD HIST PHI PART C*. 2019;73:1-9. doi:10.1016/j.shpsc.2018.05.007
11. Frieden TR. Evidence for health decision making—beyond randomized, controlled trials. *N Engl J Med*. 2017;377(5):465-475. doi:10.1056/nejmra1614394
12. Katz DL, Karlsen MC, Chung M, et al. Hierarchies of evidence applied to lifestyle Medicine (HEALM): introduction of a strength-of-evidence approach based on a methodological systematic review. *BMC Med Res Methodol*. 2019;19(1):178. doi:10.1186/s12874-019-0811-z

13. Potter JD, Jackson R. On meat, butter, and fudge. *Nutr Cancer*. 2019;72(1):1-4. doi:10.1080/01635581.2019.1703837
14. Van Norman GA. Drugs and devices: comparison of European and U.S. approval processes. *JACC: Basic Trans Sci*. 2016;1(5):399-412. doi:10.1016/j.jacbts.2016.06.003
15. CIOMS Working Group IV. *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*. Council for International Organizations of Medical Sciences;1998. Accessed May 17, 2022. https://cioms.ch/publications/product/benefit-risk-balance-for-marketed-drugs-evaluating-safety-signals/
16. Howick J, Chalmers I, Glasziou P, et al. The Oxford 2011 levels of evidence. 2011. Accessed May 17, 2022. http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf
17. Carnap R. On the application of inductive logic. *Philos Phenomenol Res*. 1947;8(1):133-148. doi:10.2307/2102920
18. CHMP Working Group. Report of the CHMP Working Group on Benefit-Risk Assessment Models and Methods Doc. Ref. EMEA/CHMP/15404/2007. 2007. Accessed May 17, 2022. https://www.ema.europa.eu/documents/regulatory-procedural-guideline/report-chmp-working-group-benefit-risk-assessment-models-methods_en.pdf
19. European Medicines Agency (Committee for Medicinal Products for Human Use). Appendix 3: Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use. In: Mussen F, Salek S, Walker S, eds. *Benefit-Risk Appraisal of Medicines: A Systematic Approach to Decision-making*. Wiley;2008:233-249.
20. De Pretis F, Landes J, Osimani B. E-synthesis: a Bayesian framework for causal assessment in pharmacosurveillance. *Front Pharmacol*. 2019;10:1317. doi:10.3389/fphar.2019.01317
21. Landes J, Osimani B, Poellinger R. Epistemology of causal inference in pharmacology. *Eur J Phil Sci*. 2018;8(1):3-49. doi:10.1007/s13194-017-0169-1
22. Abdin AY, Auker-Howlett D, Landes J, Mulla G, Jacob C, Osimani B. Reviewing the mechanistic evidence assessors E-synthesis and EBM: a case study of amoxicillin and drug reaction with eosinophilia and systemic symptoms (DRESS). *Curr Pharm Design*. 2019;25(16):1866-1880. doi:10.2174/1381612825666190628160603
23. De Pretis F, Osimani B. New insights in computational methods for pharmacovigilance: E-synthesis, a Bayesian framework for causal assessment. *Int J Environ Res Public Health*. 2019;16(12):2221. doi:10.3390/ijerph16122221
24. De Pretis F, Landes J, Peden W. Artificial intelligence methods for a Bayesian epistemology-powered evidence evaluation. *J Eval Clin Pract*. 2021;27(3):504-512. doi:10.1111/jep.13542
25. De Pretis F, Peden W, Landes J, Osimani B. Pharmacovigilance as personalized evidence. In: Beneduce C, Bertolaso M, eds. *Personalized Medicine in the Making. Philosophical Perspectives from Biology to Healthcare*. Springer International Publishing; 2022:147-170.
26. Radzvilas M, Peden W, De Pretis F. A battle in the statistics wars: a simulation-based comparison of Bayesian, Frequentist and Williamsonian methodologies. *Synthese*. 2021;199(5-6):13689-13748. doi:10.1007/s11229-021-03395-y
27. Hill AB. The environment and disease: association or causation? *J R Soc Med*. 2015;108(1):32-37. doi:10.1177/0141076814562718
28. IARC. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Preamble*. International Agency for Research on Cancer; 2006. Accessed May 17, 2022. https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/
29. Ankley GT, Bennett RS, Erickson RJ, et al. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environ Toxicol Chem*. 2010;29(3):730-741. doi:10.1002/etc.34
30. Schurz G. The hierarchy-of-hypotheses approach from a philosophy of science perspective. *BioScience*. 2020;71(4):350-356. doi:10.1093/biosci/biaa097

31. Bovens L, Hartmann S. *Bayesian Epistemology*. Oxford University Press; 2003.

32. Neapolitan RE. *Learning Bayesian Networks. Prentice Hall series in Artificial Intelligence*. Pearson Prentice Hall; 2004.

33. Swaen G, Amelsvoort vL, A weight of evidence approach to causal inference. *J Clin Epidemiol*. 2009;62(3):270-277. doi:10.1016/j.jclinepi.2008.06.013

34. Maskarinec G, Murphy S, Shumay D, Kakai H. Dietary changes among cancer survivors. *Eur J Cancer Care*. 2001;10(1):12-20. doi:10.1046/j.1365-2354.2001.00245.x

35. McCullough ML, Gapstur SM, Shah R, Jacobs EJ, Campbell PT. Association between red and processed meat intake and mortality among colorectal cancer survivors. *J Clin Oncol*. 2013;31(22): 2773-2782. doi:10.1200/jco.2013.49.1126

36. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16(16): 1599-1600. doi:10.1016/S1470-2045(15)00444-1

37. Rosato V, Negri E, Serraino D, et al. Processed meat and risk of renal cell and bladder cancers. *Nutr Cancer*. 2018;70(3):418-424. doi:10.1080/01635581.2018.1445764

38. Pournaghi SJ, Noveyri FB, Doust HM, et al. The association of consumption of animal proteins and the risk of esophageal cancer. *Nutr Cancer*. 2019;71(7):1094-1099. doi:10.1080/01635581.2019.1597903

39. De Pretis F, Landes J. EA[3]: A softmax algorithm for evidence appraisal aggregation. *PLoS One*. 2021;16(6):e0253057. doi:10.1371/journal.pone.0253057

40. Vandenbroucke JP, Psaty BM. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. *JAMA*. 2008;300(20):2417-2419. doi:10.1001/jama.2008.723

41. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet*. 2004;363(9422):1728-1731. doi:10.1016/S0140-6736(04)16261-2

42. Duijnhoven RG, Straus SMJM, Raine JM, Boer dA, Hoes AW, Bruin MLD. Number of patients studied prior to approval of new medicines: a database analysis. *PLoS Med*. 2013;10(3):e1001407. doi:10.1371/journal.pmed.1001407

43. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (Revision 3). 2014. Accessed May 17, 2022. https://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideMethStandardsPE_Rev3.pdf

44. Beasley CM, Dellva MA, Tamura RN, et al. Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. *Br J Psychiatry*. 1999;174(1):23-30. doi:10.1192/bjp.174.1.23

45. Preston TA. DES and the elusive goal of drug safety. In: Dutton DB, ed. *Worse than the Disease: Pitfalls of Medical Progress*. Cambridge University Press; 1988:31-90.

46. Food and Drug Administration. Drug induced liver injury: premarketing clinical evaluation—guidance for industry. 2009. Accessed December 15, 2021. Accessed May 17, 2022 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

47. Pirmohamed M. Drug-grapefruit juice interactions. *Br Med J*. 2013; 346:f1. doi:10.1136/bmj.f1

48. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. *PLoS Med*. 2013;10(12): e1001578. doi:10.1371/journal.pmed.1001578

49. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017. doi:10.1002/14651858.mr000033.pub3

50. White J, Bero LA. Corporate manipulation of research: strategies are similar across five industries. *Stanford Law Policy Rev*. 2010;21(1): 105-133.

51. Nestle M. Corporate funding of food and nutrition research. *JAMA Int Med*. 2016;176(1):13-14. doi:10.1001/jamainternmed.2015.6667

52. Holman B. Philosophers on drugs. *Synthese*. 2019;196(11): 4363-4390. doi:10.1007/s11229-017-1642-2

53. Jukola S. Commercial interests, agenda setting, and the epistemic trustworthiness of nutrition science. *Synthese*. 2019;198(S10): 2629-2646. doi:10.1007/s11229-019-02228-3

54. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med*. 2008;5(3):e67. doi:10.1371/journal.pmed.0050067

55. Mercuri M, Baigrie B, Upshur RE. Going from evidence to recommendations: can GRADE get us there? *J Eval Clin Prac*. 2018;24(5):1232-1239. doi:10.1111/jep.12857

56. ECETOC. Framework for the Integration of Human and Animal Data in Chemical Risk Assessment. 2009. Accessed May 17, 2022. http://www.ecetoc.org/uploads/Publications/documents/TR%20104.pdf

57. Herxheimer A. Pharmacovigilance on the turn? Adverse reactions methods in 2012. *Br J Gen Prac*. 2012;62(601):400-401. doi:10.3399/bjgp12X653453

58. Abernethy DR, Woodcock J, Lesko LJ. Pharmacological mechanism-based drug safety assessment and prediction. *Clin Pharmacol Ther*. 2011;89(6):793-797. doi:10.1038/clpt.2011.55

59. European Medicines Agency. Pharmacovigilance planning. 2006. Accessed May 17, 2022. https://www.ema.europa.eu/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-25.pdf

60. Aronson JK, Hauben M. Drug safety: anecdotes that provide definitive evidence. *Br Med J*. 2006;333(7581):1267-1269. doi:10.1136/bmj.39036.666389.94

61. Onakpoya IJ, Heneghan CJ, Aronson JK. Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis. *Crit Rev Toxicol*. 2016;46:477-489. doi:10.3109/10408444.2016.1149452

62. Edwards IR. Good pharmacovigilance practice and the curate's egg. *Drug Safety*. 2012;35(6):429-435. doi:10.2165/11634410-000000000-00000

63. Ghosh JK, Valtorta M. Building a Bayesian network model of heart disease. In: *ACM-SE 38. Proceedings of the 38th Annual on Southeast Regional Conference*. Association for Computing Machinery; 2000: 239-240.

64. Whitney CW, Lanzanova D, Muchiri C, et al. Probabilistic decision tools for determining impacts of agricultural development policy on household nutrition. *Earth Future*. 2018;6(3):359-372. doi:10.1002/2017ef000765

65. Marvin HJ, Bouzembrak Y. A system approach towards prediction of food safety hazards: impact of climate and agrichemical use on the occurrence of food safety hazards. *Agri Syst*. 2020;178:102760. doi:10.1016/j.agsy.2019.102760

66. Bouzembrak Y, Marvin HJ. Impact of drivers of change, including climatic factors, on the occurrence of chemical food safety hazards in fruits and vegetables: a Bayesian network approach. *Food Control*. 2019;97 23:67-76. doi:10.1016/j.foodcont.2018.10.021

67. Food and Agriculture Organization and World Health Organization. Principles and methods for the risk assessment of chemicals in food. 2020. Accessed May 17, 2022. https://www.who.int/publications/i/item/9789241572408

68. Greenhalgh T. Why do we always end up here? Evidence-based medicine's conceptual cul-de-sacs and some off-road alternative routes. *J Primary Health Care*. 2012;4(2):92-97. doi:10.1071/hc12092

762 WILEY—Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

69. Kastner M, Antony J, Soobiah C, Straus SE, Tricco AC. Conceptual recommendations for selecting the most appropriate knowledge synthesis method to answer research questions related to complex evidence. *J Clin Epidemiol*. 2016;73:43-49. doi:10.1016/j.jclinepi.2015.11.022

70. Tricco AC, Antony J, Soobiah C, et al. Knowledge synthesis methods for integrating qualitative and quantitative data: a scoping review reveals poor operationalization of the methodological steps. *J Clin Epidemiol*. 2016;73:29-35. doi:10.1016/j.jclinepi.2015.12.011

71. Greenhalgh T, Wong G, Westhorp G, Pawson R. Protocol -realist and meta-narrative evidence synthesis: evolving standards (RAMESES). *BMC Med Res Methodol*. 2011;11(1):115. doi:10.1186/1471-2288-11-115

72. Warren FC, Abrams KR, Golder S, Sutton AJ. Systematic review of methods used in meta-analyses where a primary outcome is an adverse or unintended event. *BMC Med Res Methodol*. 2012;12(1):64. doi:10.1186/1471-2288-12-64

73. Williamson J. Evidential proximity, independence, and the evaluation of carcinogenicity. *J Eval Clin Pract*. 2019;25(6):955-961. doi:10.1111/jep.13226

74. Rocca E. The judgements that evidence-based medicine adopts. *J Eval Clin Pract*. 2018;24(5):1184-1190. doi:10.1111/jep.12994

75. Sherman RE, Anderson SA, Pan GJD, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297. doi:10.1056/nejmsb1609216

76. Godfray HCJ, Aveyard P, Garnett T, et al. Meat consumption, health, and the environment. *Science*. 2018;361(6399):eaam5324. doi:10.1126/science.aam5324

77. Borghini A, Piras N, Serini B. Defective food concepts. Synthese; 2021;199(5-6):12225-12249. doi:10.1007/s11229-021-03330-1

78. Russo F, Williamson J. Interpreting causality in the health sciences. *Int Studies Philos Sci*. 2007;21(2):157-170. doi:10.1080/02698590701498084

79. Vandenbroucke JP, Broadbent A, Pearce N. Causality and causal inference in epidemiology: The need for a pluralistic approach. *Int J Epidemiol*. 2016;45(6):1776-1786. doi:10.1093/ije/dyv341

80. Rosato V, Tavani A, Negri E, et al. Processed meat and colorectal cancer risk: A pooled analysis of three italian case-control studies. *Nutr Cancer*. 2017;69(5):732-738. doi:10.1080/01635581.2017.1310259

81. Shayanfar M, Vahid F, Faghfoori Z, Davoodi SH, Goodarzi R. The association between index of nutritional quality (INQ) and glioma and evaluation of nutrient intakes of these patients: a case-control study. *Nutr Cancer*. 2017;70(2):213-220. doi:10.1080/01635581.2018.1412469

82. Um CY, Fedirko V, Flanders WD, Judd SE, Bostick RM. Associations of calcium and milk product intakes with incident, sporadic colorectal adenomas. *Nutr Cancer*. 2017;69(3):416-427. doi:10.1080/01635581.2017.1274408

83. Yin X, Bostick RM. Associations of nut intakes with incident sporadic colorectal adenoma: A pooled case-control study. *Nutr Cancer*. 2018;71(5):731-738. doi:10.1080/01635581.2018.1521440

84. Fereidani SS, Sedaghat F, Eini-Zinab H, et al. Gaussian graphical models identified food intake networks among iranian women with and without breast cancer: A case-control study. Nutr Cancer; 2020;73(10):1890-1897. doi:10.1080/01635581.2020.1820051

85. Ziouziou I, Shariat SF, Ajdi F, Khabbal Y. Association of processed meats and alcohol consumption with renal cell carcinoma: A worldwide population-based study. Nutr Cancer; 2020;73(11-12):2665-2670. doi:10.1080/01635581.2020.1856388

86. Ziouziou I, Touzani AM, Lahlou L, et al. Association of prostate cancer with nuts, seeds, alcohol and processed meats: A worldwide population-based study. Nutr Cancer; 2020;73(11-12):2538-2545. doi:10.1080/01635581.2020.1841250

87. Howson C, Urbach P. *Scientific Reasoning*. 3rd ed. Open Court; 2006.

88. Sprenger J, Hartmann S. *Bayesian Philosophy of Science*. Oxford University Press. 2019.

89. Crupi V, Tentori K. State of the field: measuring information and confirmation. *Studies History Philos Sci A*. 2014;47:81-90. doi:10.1016/j.shpsa.2014.05.002

90. Dawid R, Hartmann S, Sprenger J. The no alternatives argument. *Br J Philos Sci*. 2015;66(1):213-234. doi:10.1093/bjps/axt045

91. Savage LJ. *The Foundations of Statistics*. Dover Publications. 2nd ed. 1972.

92. Bradley S. Imprecise probabilities. In: Zalta EN, ed. *Stanford Encyclopedia of Philosophy*, Summer 2015 ed. 2015. http://plato.stanford.edu/entries/imprecise-probabilities

93. Spohn W. *The Laws of Belief. Ranking Theory and its Philosophical Applications*. Oxford University Press; 2012.

94. Lindley DV. The philosophy of statistics. *J R Stat Soc D*. 2000;49(3):293-337. doi:10.1111/1467-9884.00238

95. Sprenger J. The objectivity of subjective Bayesianism. *Eur J Philos Sci*. 2018;8(3):539-558. doi:10.1007/s13194-018-0200-1

96. Williamson J. *In Defence of Objective Bayesianism*. Oxford University Press. 2010.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX A:

We now provide data and methodological details in a technical appendix.

A.1 | Data from Swaen & Van Amelsvoort

The original data from Swaen & Van Amelsvoort can be found in the Supplementary material.

A.2 | Our dose–response assessments

We assessed how strongly the agents in Table A2 relevant to our study satisfied Hill's dose–response criterion. Agents for which there was evidence are collected in Table A3 and those with absence of evidence are in Table A4.

A.3 | Decoding IARC monographs and rationales

For all the agents we assessed, we here list a decoding of the variables names in Swaen & van Amelsvoort[33] (see Table A2). Additionally, for each agent we provide the relevant IARC monographs, including the corresponding URL of the latest, and in case there is some evidence we also give a verbatim quote supporting our assessment. Finally, we list either and the assessed degree of dose response or conclude that there is absence of evidence.

TABLE A1 IARC Group 1 agents with (some) evidence of a dose response according to Swaen and van Amelsvoort.[33]

Chemical	Strength	Consistency	Specificity	Temporality	Dose response	Plausibility	Coherence	Experimental	Analogy
Aflatoxin	90	40	90	100	90	90	60	0	0
Alcoholic beverages	80	90	40	100	90	80	80	0	0
Aluminium p	60	60	60	100	30	80	20	0	60
Aminobiph	80	40	80	100	50	50	0	0	0
Arecanut	95	95	90	100	95	90	95	0	0
Arsenic	80	80	90	100	95	80	0	0	70
ars dr.w	60	80	70	100	70	50	70	80	60
Asbestos	100	95	40	100	100	90	95	0	0
Benzene	95	95	95	100	95	70	80	85	0
Benzidine	95	95	80	100	30	90	50	0	50
Benzoapyrene	60	95	85	100	95	80	75	50	0
Berylium	60	50	60	100	60	20	70	0	40
Betel quid	85	90	90	100	90	80	80	0	40
Betel + tab	95	90	90	100	90	70	80	0	60
Bischlmether	90	90	95	100	50	40	0	0	0
Cadmium	60	40	60	100	30	70	0	0	20
Chlorambucil	80	80	80	100	60	80	80	0	80
ChromiumVI	95	95	80	100	95	80	80	0	80
Cokeovens	95	95	60	100	80	80	80	0	80
oestrogen.ther	60	60	90	100	60	80	0	0	60
estrog.oralcon	60	80	80	100	60	80	0	0	60
estr.ster	95	90	80	100	80	80	0	0	60
Ethyleneoxid	60	50	30	100	60	90	60	0	0
Formaldehyde	80	70	80	100	30	80	60	0	0
Furniture	95	70	50	100	30	20	60	0	0
Gamma rad	95	80	80	100	80	80	80	0	60
Inv.smoke	60	80	80	100	70	80	0	0	80
Iron&steel	95	80	80	100	80	40	30	0	0
Melphalan	95	80	80	100	60	80	80	60	60
MOPP	95	95	90	100	60	80	0	0	60
2-naphtyl	95	95	95	100	60	70	60	60	60
Nickel	95	95	95	100	95	80	60	0	60
Oral contracept	95	80	60	50	30	80	0	0	0
Phenacitin mix	95	90	90	100	80	70	0	0	0
Plutonium	60	40	60	100	40	80	60	0	80
rad.iodine	95	95	95	100	90	90	90	0	60
alf.emit	95	80	60	100	60	80	0	0	60
beta.emit	95	80	60	100	60	80	0	0	80
Radium 3x	95	80	60	100	60	90	0	0	80

(Continues)

764 | WILEY— Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

TABLE A1 (Continued)

Chemical	Strength	Consistency	Specificity	Temporality	Dose response	Plausibility	Coherence	Experimental	Analogy
Radon	60	80	80	100	80	80	0	0	80
Silica	80	60	95	100	95	80	80	0	0
Soots	95	80	70	100	60	80	0	0	80
Tamoxifen	95	60	60	100	60	80	0	0	60
tcdd	60	40	30	100	60	80	0	0	0
Thorium	90	90	95	100	90	90	0	0	80
tobacco.sm	95	95	80	100	95	90	80	95	80
VCM	95	90	60	100	60	70	0	50	0
X&gamma	95	80	80	100	80	90	60	80	60

Abbreviation: IARC, International Agency for Research on Cancer.

TABLE A2 IARC Group 1 agents with evidence of absence or absence of evidence of a dose response according to Swaen and van Amelsvoort[33]

Agent	Strength	Consistency	Specificity	Temporality	Dose response	Plausibility	Coherence	Experimental	Analogy
aurim.manuf	95	70	80	100	0	90	0	80	0
Azathioprine	80	60	60	100	0	40	0	0	20
Nbischlonaph	95	40	80	100	0	80	80	40	80
Boot + shoe	95	80	70	100	0	20	60	0	0
Cutanediol	90	20	80	100	0	80	20	0	40
Cemustine	95	80	80	100	0	80	0	0	60
Chimny s	80	40	40	100	0	40	20	0	0
Cyclosporin	95	80	60	100	0	40	0	0	60
Coal gassif	95	80	80	100	0	80	80	0	90
coal.t.dest	60	60	80	100	0	80	0	0	90
Coaltarp	95	60	80	100	0	80	0	0	80
Cyclophos	95	70	70	100	0	80	80	0	80
des	95	80	95	100	0	80	90	0	60
Epstein–Barr	95	60	90	100	0	50	0	0	0
Erionite	95	80	80	100	0	90	40	0	80
estro.nonst	95	80	95	100	0	80	0	0	60
Etopiside + pl	80	60	80	100	0	80	60	0	60
Gallium ars	0	0	0	0	0	70	0	0	60
haemat.min	95	60	80	100	0	40	60	40	0
helicib.pyl	95	90	90	100	0	60	80	30	0
Hep.b	95	95	90	100	0	50	60	0	0
hep.c	95	60	80	100	0	50	60	0	0
herb.rem	40	40	90	100	0	80	80	0	0
HIV	95	95	90	100	0	50	0	0	0
HPV	80	80	80	100	0	80	60	0	0

TABLE A2 (Continued)

Agent	Strength	Consistency	Specificity	Temporality	Dose response	Plausibility	Coherence	Experimental	Analogy
Htcel l	60	50	60	100	0	70	0	0	0
Isopropalc	20	0	40	100	0	50	0	0	0
magenta.man	95	60	80	100	0	80	0	80	60
8muthozy	95	80	60	100	0	80	0	0	60
min.oils	95	60	60	100	0	80	0	0	0
Mustard gas	95	90	90	100	0	70	60	0	0
Neutrons	95	80	95	100	0	80	0	0	60
n.nitrosonic	0	0	0	0	0	80	0	0	60
opishor.inf	95	90	90	100	0	90	80	0	0
Painter	50	50	50	100	0	30	0	0	0
Paving/roofing	60	70	80	100	0	80	0	0	60
Phosphorous32	60	50	80	100	0	80	0	0	0
rubber.ind	60	60	30	100	0	30	0	0	0
salt.fish	80	80	80	100	0	30	0	0	0
Schistosoma	95	95	95	100	0	0	80	0	0
Shale oil	95	90	90	100	0	80	0	0	60
Solar rad	95	80	60	100	0	80	60	0	60
smokl.tob	95	95	90	100	0	60	80	0	0
Strong mists	80	60	80	100	0	60	0	0	0
talc.asbest	60	60	40	100	0	80	80	0	80
Thiotepa	80	80	80	100	0	80	90	0	80
Treosulfan	95	30	60	100	0	80	0	0	60
Wooddust	95	80	80	100	0	90	0	0	0

Note: Both these absences are represented by the column of zeros.

TABLE A3 Sixty-eight IARC Group 1 agents relevant to our study for which IARC reported sufficientevidence to assess the strength of (a possible) dose–response relationship

Agent	CAS no.	Volume	Year	Dose response
Acid mists, strong inorganic		54, 100F	2012	*100
Aristolochic acid, plants containing	313-67-7	82, 100A	2012	*100
Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	1332-21-4,12172-73-5,12001-29-5,12001-28-4	14, Sup 7, 100C	2012	100
Coal-tar pitch	65996-93-2	35, Sup 7, 100F	2012	*100
Cyclophosphamide	50-18-0,6055-19-2	26, Sup 7, 100A	2012	*100
Etoposide in combination with cisplatin and bleomycin	33419-42-0, 15663-27-1, 11056-06-7	76, 100A	2012	*100
Methoxsalen (8-methoxypsoralen) plus ultraviolet A radiation	298-81-7	24, Sup 7, 100A	2012	*100
N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	16543-55-8, 64091-91-4	Sup 7, 89, 100E	2012	*100

(Continues)

766 | WILEY—Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

TABLE A3   (Continued)

Agent	CAS no.	Volume	Year	Dose response
Phosphorus-32, as phosphate	14596-37-3	78, 100D	2012	*100
Radium-224 and its decay products	13233-32-4	78, 100D	2012	100
Radium-226 and its decay products	13982-63-3	78, 100D	2012	100
Radium-228 and its decay products	15262-20-1	78, 100D	2012	100
Semustine [1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, Methyl-CCNU]	13909-09-6	Sup 7, 100A	2012	*100
Shale oils	68308-34-9	35, Sup 7, 100F	2012	*100
Sulfur mustard	505-60-2	9, Sup 7, 100F	2012	*100
Talc containing asbestiform fibres	14807-96-6	42, Sup 7	1987	*100
Tobacco, smokeless		Sup 7, 89, 100E	2012	*100
Arecanut		85, 100E	2012	95
Arsenic and inorganic arsenic compounds	7440-38-2	23, Sup 7, 100C	2012	95
Benzene	1-43-2	29, Sup 7. 100F, 120	2018	95
Benzo[a]pyrene	50-32-8	Sup 7, 92, 100F	2012	95
Chromium (VI) compounds	18540-29-9	Sup 7, 49, 100C	2012	95
Nickel compounds		Sup 7, 49, 100C	2012	95
Silica dust, crystalline, in the form of quartz or cristobalite	14808-60-7	Sup 7, 68, 100C	2012	95
Tobacco smoking		83, 100E	2012	95
Aflatoxins	1402-68-2	Sup 7, 56, 82, 100F	2012	90
Alcoholic beverages		44, 96, 100E	2012	90
Betel quid with tobacco		Sup 7, 85, 100E	2012	90
Betel quid without tobacco		Sup 7, 85, 100E	2012	90
Mineral oils, untreated or mildly treated		33, Sup 7, 100F	2012	*90
Radioiodines, including iodine-131		78, 100D	2012	90
Thorium-232 and its decay products	7440-29-1	78, 100D	2012	90
Coke production		Sup 7, 92, 100F	2012	80
Iron and steel founding (occupational exposure during)		34, Sup 7, 100F	2012	80
Phenacetin, analgesic mixtures containing		Sup 7, 100A	2012	80
Radon-222 and its decay products	10043-92-2	43, 78, 100D	2012	80
X- and Gamma-Radiation		75, 100D	2012	80
Gallium arsenide	1303-00-0	86, 100C	2012	*70
Neutron radiation		75, 100D	2012	*70
Thiotepa	52-24-4	Sup 7, 50, 100A	2012	*70
Tobacco smoke, second-hand		83, 100E	2012	70
Treosulfan	299-75-2	26, Sup 7, 100A	2012	*70
2,3,7,8-Tetrachlorodibenzo-para-dioxin	1746-01-6	Sup 7, 69, 100F	2012	60
2-Naphthylamine	91-59-8	4, Sup 7, 99, 100F	2012	60
Beryllium and beryllium compounds	7440-41-7	Sup 7, 58, 100C	2012	60

TABLE A3 (Continued)

Agent	CAS no.	Volume	Year	Dose response
Chlorambucil	305-03-3	26, Sup 7, 100A	2012	60
Oestrogen therapy, postmenopausal		72, 100A	2012	60
Oestrogen-progestogen oral contraceptives (combined)		72, 91, 100A	2012	60
Ethylene oxide	75-21-8	Sup 7, 60, 97, 100F	2012	60
Melphalan	148-82-3	9, Sup 7, 100A	2012	60
MOPP and other combined chemotherapy including alkylating agents		Sup 7, 100A	2012	60
Radionuclides, alpha-particle-emitting, internally deposited		78, 100D	2012	60
Radionuclides, beta-particle-emitting, internally deposited		78, 100D	2012	60
Soot (as found in occupational exposure of chimney sweeps)		35, Sup 7, 92, 100F	2012	60
Tamoxifen	10540-29-1	66, 100A	2012	60
Vinyl chloride	75-01-4	Sup 7, 97, 100F	2012	60
1,3-Butadiene	106-99-0	Sup 7, 54, 71, 97, 100F	2012	*50
4-Aminobiphenyl	92-67-1	1, Sup 7, 99, 100F	2012	50
Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	542-88-1,107-30-2	4, Sup 7, 100F	2012	50
Diethylstilbestrol	56-53-1	21, Sup 7, 100A	2012	*50
Solar radiation		55, 100D	2012	*50
Plutonium	7440-07-5	78, 100D	2012	40
Salted fish, Chinese-style		56, 100E	2012	*40
Aluminium production		34, Sup 7, 92, 100F	2012	30
Benzidine	92-87-5	29, Sup 7, 99, 100F	2012	30
Cadmium and cadmium compounds	7440-43-9	58, 100C	2012	30
Formaldehyde	50-00-0	Sup 7, 62, 88, 100F	2012	30
Wood dust		62, 100C	2012	30

Note: Agents are ordered by the assessed strengths. Starred estimates originate from authors, nonstarred estimates are taken from Swaen & van Amelsvoort[33] (see Table A1). Further classification is provided through CAS numbers, volumes and related years. The former are unique numerical identifiers assigned to every chemical substance by the CAS, a division of the American Chemical Society. The latter refer to the IARC monographs where the agents are studied, with years pointing to the most recent publications in print.

Abbreviations: CAS, Chemical Abstracts Service; IARC, International Agency for Research on Cancer.

TABLE A4 Twenty-five IARC Group 1 agents relevant to our study for which IARC reported absence of evidence

Agent	CAS no.	Volume	Year
Auramine production		Sup 7, 99, 100F	2012
Azathioprine	446-86-6	26, Sup 7, 100A	2012
Boot and shoe manufacture and repair		25, Sup 7	1987
Chlornaphazine	494-03-1	4, Sup 7, 100A	2012
Coal gasification		Sup 7, 92, 100F	2012

768 | **WILEY**— Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

TABLE A4 (Continued)

Agent	CAS no.	Volume	Year
Coal-tar distillation	8007-45-2	92, 100F	2012
Cyclosporine	59865-13-3,79217-60-0	50, 100A	2012
Epstein-bar virus		70, 100B	2012
Erionite	6733-21-9	42, Sup 7, 100C	2012
Oestrogen-progestogen menopausal therapy (combined)		72, 91, 100A	2012
Haematite mining (underground)		1, Sup 7, 100D	2012
Helicobacter pylori (infection with)		61, 100B	2012
Hepatitis B virus (chronic infection with)		59, 100B	2012
Hepatitis C virus (chronic infection with)		59, 100B	2012
Human immunodeficiency virus type 1 (infection with)		67, 100B	2012
Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59		64, 90, 100B	2012
Human T-cell lymphotropic virus type I		67, 100B	2012
Isopropyl alcohol manufacture using strong acids		Sup 7, 100F	2012
Magenta production		Sup 7, 57, 99, 100F	2012
Opisthorchis viverrini (infection with)		61, 100B	2012
Painter (occupational exposure as a)		47, 98, 100F	2012
Paving and roofing with coal-tar pitch		35, Sup 7, 92, 100F	2010
Rubber manufacturing industry		28, Sup 7, 100F	2012
Schistosoma haematobium (infection with)		61, 100B	2012
Soot (as found in occupational exposure of chimney sweeps)		35, Sup 7, 92, 100F	2012

Note: The information was retrieved from Table A2 and these agents were omitted from our study. Similar to Table A3, for each agent proper CAS number, volume and year are reported.

Abreviations: CAS, Chemical Abstracts Service; IARC, International Agency for Research on Cancer.

- aurim.manuf: Auramine and auramine production. Auramine production 1 Sup 7, 99, 100F 2012. No dose–response information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-12.pdf—absence of evidence.
- Azathioprine: 446-86-6 Azathioprine 1 26, Sup 7, 100A 2012. No dose–response information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100A-20.pdf—absence of evidence.
- Nbischlonaph–Chlornaphazine: 494-03-1 Chlornaphazine 1 4, Sup 7, 100A 2012. No dose–response information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100A-21.pdf—absence of evidence.
- boot + shoe—Boot and shoe manufacture and repair: Boot and shoe manufacture and repair (see Leather dust, Benzene) 25, Sup 7 1987. 'Occupational exposure'—absence of evidence.
- Butanediol—1,3-Butadiene: 106-99-0 1,3-Butadiene 1 Sup 7, 54, 71, 97, 100F 2012. 'A statistically significant dose–response trend was noted for all leukaemia. [...] Among men there was no indication of an increased risk for lung cancer and no evidence for an internal dose–response. Among women there was evidence of an increased risk for lung cancer, although there was no evidence for an internal dose–response in the exposed group. [...] Overall, the epidemiological evidence from the styrene-butadiene and the butadienemonomer industries clearly indicates an increased risk for haematolymphatic malignancies. Studies from the styrene-butadiene industry show an excess of leukaemia, and a dose–response relationship with cumulative exposure to butadiene, while studies from the monomer industry show an excess of haematolymphatic malignancies in general, attributable both to leukaemia and malignant lymphoma'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-26.pdf at p. 312—assessed degree of dose–response relationship 50.

- Semustine—Methyl-CCNU: 13909-09-6 Semustine [1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, Methyl-CCNU] 1 Sup 7, 100A 2012. 'A subsequent report described a strong dose–response relationship, adjusted for survival time, giving a relative risk of almost 40 among patients who had received the highest dose'. https://publications.iarc.fr/118 at p. 58—assessed degree of dose–response relationship 100.

- Chimny s—Chimney sweeping, that is, soot (s found in occupational exposure of chimney sweeps): Chimney sweeping (see Soot) 92 2010. 'Occupational exposure'—absence of evidence.

- Cyclosporin–Cyclosporine. 59865-13-3, 79217-60-0 Cyclosporine 1 50, 100A 2012. No dose–reponse information or not sufficient dose–response information. https://publications.iarc.fr/_publications/media/download/5195/47e16232b61bbce71c149f (…)—absence of evidence.

- Coal Gassif–Coal Gasification: Coal gasification 1 Sup 7, 92, 100F 2012. No dose–reponse information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-15.pdf—absence of evidence.

- Coal.t.dest—Occupational exposures during coal-tar distillation: 8007-45-2 Coal-tar distillation 1 92, 100F 2012. No dose–reponse information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-16.pdf—absence of evidence.

- Coaltarp—Coal-tar pitch: 65996-93-2 Coal-tar pitch 1 35, Sup 7, 100F 2012. 'When the workers were stratified by 1-hydroxypyrene excretion in the urine, the amount of DNA strand-breaks in their leukocytes increased, and the 8-oxo-dG/dG ratio decreased in a dose-dependent manner'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-17.pdf at p. 165—assessed degree of dose–response relationship 100.

- Cyclophos—Cyclophosphamide: 50-18-0, 6055-19-2 Cyclophosphamide 1 26, Sup 7, 100A 2012. '[...] and a case-control study of leukaemia following ovarian cancer in the former German Democratic Republic where a strong dose–response relationship was observed'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100A-9.pdf at p. 66—assessed degree of dose–response relationship 100.

- Des—Diethylstilbestrol: 56-53-1 Diethylstilbestrol 1 21, Sup 7, 100A 2012. 'The pituitary growth response of the diethylstilbestrol-treated (5 mg at 63 ± 4 days until 12 weeks of age) in F1 (COPxACI) rats was intermediate (6.9-fold) to that exhibited by the parental ACI and COP strains'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100A-16.pdf at p. 190—assessed degree of dose–response relationship 50.

- Epstein-bar—Epstein-Barr virus: Epstein-Barr virus 1 70, 100B 2012. 'Infectious condition'—absence of evidence.

- Erionite: No dose–response information or not sufficient dose–response information. https://publications.iarc.fr/_publications/media/download/5227/44041c781b3b6eb52ad87 (…)—absence of evidence.

- estro.nonst—Oestrogen-progestogen menopausal therapy (combined): Oestrogen-progestogen menopausal therapy (combined) 1 72, 91, 100A 2012. No dose–reponse information or not sufficient dose–response information. https://publications.iarc.fr/118—absence of evidence.

- etoposide + pl—Etoposide in combination with cisplatin and bleomycin: 33419-42-0, 15663-27-1, 11056-06-7. Etoposide in combination with cisplatin and bleomycin 1 76, 100A 2012. 'The risk for leukemia increased strongly with cumulative dose of etoposide in multivariate analyses'. https://publications.iarc.fr/118 at p. 99—assessed degree of dose–response relationship 100.

- Gallium ars—Gallium Arsenide. 1303-00-0 Gallium arsenide (see Arsenic and inorganic arsenic compounds) 86, 100C 2012. 'In female rats, dose-related responses were reported for the incidence of lung alveolar/bronchiolar tumours and atypical hyperplasia of the alveolar epithelium. In male rats, though treatment-related tumours were not observed, a dose-related increase in the incidence of atypical hyperplasia of the lung alveolar epithelium occurred'. https://publications.iarc.fr/120 at pp. 76–79—assessed degree of dose–response relationship 75.

- haemat.min—Haematite mining (underground): Haematite mining (underground) 1 1, Sup 7, 100D 2012. Occupational exposure—absence of evidence.

- elicib.pyl—Helicobacter pylori (infection with): 1 61, 100B 2012. 'Infectious condition'—absence of evidence.

- Hep.b–Hepatitis B virus (chronic infection with): Hepatitis B virus (chronic infection with) 1 59, 100B 2012. 'Infectious condition'—absence of evidence.

- Hep.c—Hepatitis C virus (chronic infection with): Hepatitis C virus (chronic infection with) 1 59, 100B 2012. 'Infectious condition'—absence of evidence.

- Herb.rem—Aristolochia (herbal medicine), Plants containing Aristolochic acid. 313-67-7 Aristolochic acid, plants containing 1 82, 100A 2012. 'Oral administration of aristolochic acid to rats caused a dose- and time-dependent tumour response'. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Pharmaceuticals-2012 at p. 357—assessed degree of dose–response relationship 100.

- HIV—Human immunodeficiency virus type 1 (infection with). Human immunodeficiency virus type 1 (infection with) 1 67, 100B 2012. 'Infectious condition'—absence of evidence.

- HPV—Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59: Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 1 64, 90, 100B 2012. 'Infectious condition'—absence of evidence.

- Htcel 1—Human T-cell lymphotropic virus type I (HTLV-I). Human T-cell lymphotropic virus type I 1 67, 100B 2012. 'Infectious condition'—absence of evidence.

- isopropalc—Isopropyl alcohol manufacture by the strong-acid process. Isopropyl alcohol manufacture using strong acids 1 Sup 7, 100F 2012. No dose–response information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-32.pdf—absence of evidence.

770 | WILEY—Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

- magenta.man—Magenta and magenta production: Magenta production 1 Sup 7, 57, 99, 100F 2012. No dose–response information or not sufficient dose–response information. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-13.pdf—absence of evidence.

- red8muthozy—Methoxsalen plus ultraviolet A radiation: 298-81-7 Methoxsalen (8-methoxypsoralen) plus ultraviolet A radiation 1 24, Sup 7, 100A 2012. 'The studies that undertook analyses by level of exposure to PUVA found dose-related increases in the incidence of squamous cell carcinoma'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100A-24.pdf at p. 365—assessed degree of dose–response relationship 100.

- Mineral oils: Mineral oils, untreated or mildly treated 1 33, Sup 7, 100F 2012. 'Dose-related increase with p-value < 0.01. [...] No comparison with unused oil, but the strong dose–response and the large number of animals per group are noted'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-19.pdf at p. 185—assessed degree of dose–response relationship 90.

- Mustard Gas: 505-60-2 Sulfur mustard 1 9, Sup 7, 100F 2012. 'There was evidence of a dose–response relationship between exposure to mustard gas and subsequent development of respiratory cancer'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-30.pdf at p. 439—assessed degree of dose–response relationship 100.

- Neutron Radiation: Neutron radiation 1 75, 100D 2012. 'Neutron radiation has clear carcinogenic effects in a variety of experimental animal studies in mice, rats and monkeys. [...] There is also evidence of an increased incidence of tumours as a function of dose in several studies in mice and one new study in rats. [...] There is inadequate evidence in humans for the carcinogenicity of neutron radiation. There is sufficient evidence in experimental animals for the carcinogenicity of neutron radiation'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100D-8.pdf at p. 237—assessed degree of dose–response relationship 70.

- n.nitrosonic—N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. 16543-55-8, 64091-91-4 N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) 1 Sup 7, 89, 100E 2012. 'Two molecular epidemiology studies investigated the relationship of NNK to lung cancer in smokers using nested case-control designs. In one, urinary levels of NNAL plus its glucuronides (total NNAL), metabolites of NNK, were significantly associated with risk for lung cancer in a dose-dependent manner'. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Personal-Habits-And-Indoor-Combustions-2012 at pp. 321–322—assessed degree of dose–response relationship 100.

- opishor. inf—*Opisthorchis viverrini* (infection with): *Opisthorchis viverrini* (infection with) 1 61, 100B 2012. 'Infectious condition'—absence of evidence.

- painter—Painter (occupational exposure as a): Painter (occupational exposure as a) 1 47, 98, 100F 2012. 'Occupational exposure'—absence of evidence.

- Paving/roofing—Paving and roofing with coal-tar pitch (see Coal-tar pitch): Paving and roofing with coal-tar pitch (see Coal-tar pitch) 35, Sup 7, 92, 100F 2010. 'Occupational exposure'—absence of evidence.

- phosphorous32—Phosphorus-32: 14596-37-3 Phosphorus-32, as phosphate 1 78, 100D 2012. 'Furthermore, the risk of leukemia increased with increasing doses of 32-P'. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Radiation-2012 at p. 287—assessed degree of dose–response relationship 100.

- rubber.ind—Rubber manufacturing industry. Rubber manufacturing industry 1 28, Sup 7, 100F 2012. 'Occupational exposure'—absence of evidence.

- salt.fish—Chinese-style salted fish: Salted fish, Chinese-style 1 56, 100E 2012. 'A dose–response relationship was found in two smaller studies, with odds ratios ranging from 3.4 to 5.7 in the most exposed individuals (salted fish at least three times/week). [...] In a Southern Chinese population an increased risk for oesophageal cancer was associated with adult salted fish consumption in women, but not in men, and there was no dose–response relationship from both sexes combined'. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Personal-Habits-And-Indoor-Combustions-2012 at pp. 505–506—assessed degree of dose–response relationship 40.

- Schistosoma - Schistosoma haematobium (infection with). Schistosoma haematobium (infection with) 1 61, 100B 2012. 'Infectious condition'—absence of evidence.

- Shale oil—Shale oils: 68308-34-9 Shale oils 1 35, Sup 7, 100F 2012. 'Crude shale oil and its aromatic fractions were enclosed in bee's wax pellets—which allow slow release of the content—and implanted in the lungs of rats. The substances induced a dose-dependent increase in lung cancer (epidermoid carcinomas)'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-20.pdf at pp. 199–202—assessed degree of dose–response relationship 100.

- Solar rad—Natural sunlight: Solar radiation 1 55, 100D 2012. 'The dose–response relationship with recalled average annual hours spent in outdoor activities was incosistent. [...] Risk was increased with cumulative sun exposure in outdoor work during the summer months, but without any dose–response (OR 11.7-12.7; with wide confidence intervals). [...] In the other two, which were more recent and had better measures of exposure than many previous studies, one study related only to occupational sun exposure and showed a strong association with a dose–response relationship, and the strongest association seen in the other was with occupational sun exposure and showed evidence of a dose–response relationship'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100D-6.pdf at pp. 42–43, 62—assessed degree of dose–response relationship 50.

- smokl.tob—Smokeless tobacco: Tobacco, smokeless 1 Sup 7, 89, 100E 2012. 'Dose–response relationships were observed in several studies. [...] Strong dose–response relationships have been

observed in studies in the USA with intensity and duration of use of smokeless tobacco, snuff or chewing tobacco'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100E-8.pdf at pp. 280, 283—assessed degree of dose–response relationship 100.

- Strong mists—Mists from strong inorganic acids. Acid mists, strong inorganic 1 54, 100F 2012. 'Soskolne et al. (1992) assessed the duration and intensity of exposure to sulfuric acid among laryngeal cancer cases in a case-control study in Canada and found a dose–response progression from 10 years of probable exposure (OR, 1.97; 95%CI: 0.6–6.1) to >10 years of substantial exposure (OR, 5.6; 95%CI: 2.0–15.5)'. https://publications.iarc.fr/_publications/media/download/3076/73443059d4ec0adde7332 (…) at p. 492—assessed degree of dose–response relationship 100.

- talc.asbest—Talc containing asbestiform fibres (see Asbestos): 1332-21-4, 12172-73-5, 12001-29-5, 12001-28-4. Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) 1 14, Sup 7, 100C 2012. 'From IARC List of Classification, additional information for Asbestos: Mineral substances (e.g., talc or vermiculite) that contain asbestos should also be regarded as carcinogenic to humans'. Repeated entry from Table A1. See Asbestos.

- Thiotepa: 52-24-4 Thiotepa 1 Sup 7, 50, 100A 2012. 'This study, which used a case-control methodology within a cohort of women treated for ovarian cancer, found a strong association between the risk for leukaemia and treatment with thiotepa with a relative risk of 8.3 in the lower dose group (*n* = 4), and 9.7 in the higher dose group (*n* = 5). […] The increase in the incidence of forestomach papillomas was dose-dependent in rasH2 mice (Yamamoto et al., 1998a, b). [The Working Group noted the limited reporting of the study, i.e., no tumour incidences were provided.]'. https://publications.iarc.fr/_publications/media/download/5187/1c461f2a92d04f2f5da5dbb (…) at pp. 164, 166—assessed degree of dose–response relationship 70.

- Treosulfan: 299-75-2 Treosulfan 1 26, Sup 7, 100A 2012. 'In an international case-control study of women treated for ovarian cancer, Kaldor et al. (1990) found that the relative risk was 3.6 in the group treated with the lowest dose of treosulfan, and 33.0 within the highest dose group. [The Working Group noted that there may have been an overlap between the two studies, as the case-control study included Denmark, and covered a similar time period as the Danish cohort study.]'. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100A-15.pdf at p. 172—assessed degree of dose–response relationship 70.

- wooddust—Wood dust. Wood dust 1 62, 100C 2012. Repeated entry from Table A1. See Furniture and cabinet making.

A.4 | A primer on Bayesian reasoning

We now briefly introduce key elements of the Bayesian approach to uncertain inference.

1) Bayesian approaches interpret probabilities as an agent's rational degrees of belief. The probabilities represent the agent's knowledge, beliefs and evidence. The probabilities are thus epistemic in that they represent an agent's view of the world and not necessarily the actual world. Probabilities can be elicited and interpreted via betting scenarios: the betting quotient at which a rational agent is willing to buy and sell bets on a proposition of interest is her probability of that proposition. Unlike in Bayesian statistics, propositions of interest are not limited to (parts of) statistical models.[87,88]

2) To adopt a probability Bayesian agents fix a finite set of elementary events Ω. Propositions of interest are then identified with subsets of Ω. An initial, prior, probability function is then adopted by the agent, which takes her background knowledge (e.g., theory and expert opinion) into account but not the evidence that she later learns. The prior probability function represents the agent's belief at an very early stage of her epistemic life. To set these probabilities we first learn how to set them in rather uncontroversial settings (e.g., die rolls and roulette) and later move to more realistic problems.

3) Evidence the agent acquires is then used to update her beliefs. In case the evidence is certain, the agent learns that the actual world is surely within some nonempty subset $F \subset \Omega$, probabilities are updated by conditionalization. In case the evidence is uncertain, the agent learns that the actual world is in F with probability $0 < p < 1$, Jeffrey updating is used. The belief updates produce posterior probabilities.

4) Confirmation tracks how the posterior probability of a hypothesis of interest changes with the agent acquiring new evidence. The most popular and simple way to measure confirmation is to consider the difference between prior and posterior probability of the hypothesis, although other measures continue to attract interests.[89]

5) Evidence of absence means that the agent has information which decreases the probability that the hypothesis of interest is true. Conversely, absence of evidence means that the agent does not possess evidence that makes the hypothesis of interest more or less likely. Clearly, evidence of absence and absence of evidence have to be distinguished in a Bayesian setting. Although, absence of evidence leaves the relevant probabilities unchanged, there is a growing consensus that confirmation via nonempirical considerations is possible.[90]

6) Decisions are made by performing the act that maximizes expected utility. The agent first determines a finite set of possible acts A. Every ordered pair of an act a and a possible world ω is then assigned some utility, $u(a, \omega) \in \mathbb{R}$. The expected utility of act a is then $\sum_{\omega \in \Omega} P(\omega) u(a, \omega)$. Acting in a way that maximises expected utility is deemed rational, acting in a way that affords the agent less expected utility is considered irrational.[91]

7) E-Synthesis applies the Bayesian approach. The probabilities represent an agent's degrees of belief aiming to determine a probability that eating processed meat causes cancer. The set of elementary events is generated by the set of variables used to reason about this probability. Evidence comes in the form of studies. Confirmation is reported in Table 3. Evidence of absence

772 | WILEY— Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

DE PRETIS ET AL.

needs to differentiated from absence of evidence; we hence could not simply copy the assessment scheme of Swaen & van Amelsvoort.[33]

8) Common objections to the Bayesian approach and counter-arguments are now briefly considered.

i) Objection: The Bayesian approach falsely offers a precise real number as a probability of a hypothesis the inquiring agent remains unsure about. These probabilities appear out of thin air. Counter-argument: Bayesian probabilities are a representation of an agent's state of mind given a prior belief and an updating procedure for acquired evidence. Bayesian probabilities are not necessarily objective nor do they necessarily track the truth. The fact that a single real number is assigned to a hypothesis of interest is owed to the choice of representing rational degrees of belief. The posterior probability function depends on the choice of Ω and the prior.

ii) Objection: The Bayesian approach does not make all information explicit and fails to take all information into account. Counter-argument: It is true that not all information is made explicit. In general, choosing a small event space, Ω, entails that a great deal of information remains implicit in the prior probability function. Furthermore, it is simply infeasible to build models that can take all information explicitly into account. This infeasibility besets all formal models of uncertain inference. The quality of the inferences does, in general, depend on the quality of the underlying event space. It is hence important to adopt an appropriate event space.

iii) Objection: A single probability function is not an appropriate model of rational degrees of belief. There are two main competitors to the Bayesian approach: i) the imprecise probabilities approaches uses sets of probability functions, rather than a single probability function, to model degrees of belief.[92] ii) Ranking functions are used to avoid having to attach precise numbers to uncertain events.[93]

iv) Objection: The Bayesian approach is hopelessly subjective. Counter-arguments: (i) Bayesian probabilities are based—to the best of the agent's abilities—on her information. These probabilities hence represent the agent's considered judgements.[94] (ii) In realistic cases, subjectivity is not going to make a large difference to the posterior and the Bayesian approach is virtuous in other important senses.[95] (iii) The choice of a prior ought to be an objective one, which can be achieved by an application of a principle of entropy maximization.[96] (iv) The subjectivity can be investigated and reduced by performing numerical sensitivity analyses.