Maria Laura Ilardo, Marta Bertolaso

Exploring the Interplay of Causality Notions & Risk Concepts: Epistemological Implications

1. *Introduction*

Risk is a contextual unwanted harmful event or condition, susceptible to uncertainty (Rosa 1998), associated with variability in future outcomes, and is intricately intertwined with causality, which shapes beliefs, influencing risk perception and decisions. According to ISO 31000 (2018) «risk is the effect of uncertainty on objectives», encompassing the likelihood of either positive or negative deviations from the expected objectives. Individuals and organizations seek to analyze risk to make informed decisions and reduce the likelihood of harmful events.

Risk analysis falls within the scope of safety management and concerns understanding the world (in relation to risk), determining how we can, and should, comprehend, assess, characterize, and govern its complexities (Aven, Zio 2014; Aven 2016; SRA 2015).

The understanding of risk, its nature, perception, and management is ever changing in the context of modern society, where «different understandings of complexity led to different risk evaluations» (Rocca, Andersen 2017). In addition to traditional risks (e.g., those related to the industrial environment, the production of goods), there are "new types of risks" (e.g. those associated with technological progress and globalized processes), often characterized by scientific uncertainty (e.g., where cause and effect are not (fully) understood), difficulties in objective assessment, and the awareness that human actions can have global and long-term impacts (e.g., economic crises, climate change, pandemics). The growing awareness and concern for more complex, unpredictable, and difficult-to-control risks characterizes the notion of "risk society" (Beck 1992).

DOI: 10.4454/d4tt6h64

When conducting *risk assessment* – whether in fields like healthcare, engineering, finance, and safety more generally –, *potential risks*[1] are integral part of the proactive process of risk management. Emerging risks pose challenges to traditional approaches in risk assessment and management such as (i) their often-unpredictable nature due to lack of *a priori* evidence, (ii) their large and far-reaching harmful impacts with the potential to trigger additional hazards over time, and (iii) their often-unknown origins, evolution, and final form, rendering them poorly understood and ill-defined, thus requiring careful consideration in addressing them (Smith, Fischbacher 2009). Given these complexities, it becomes crucial to focus on how these events are comprehended, conceptualized, and addressed. These new forms of risk also underscore the interconnected nature of risk and causality, revealing how discrete events can act as catalysts for additional challenges within an often intricately interwoven system (Smith, Fischbacher 2009). Causality is the link between events and their consequence (Gianti *et al.* 2016), and proper causality assessment (CA) is key in *risk assessment*, aiming to identify causes and contributing factors and to determine the likelihood of *identified risks*[2] (Pearl 2000), thereby informing *more effective, targeted, and socially sustainable risk mitigation strategies*.

The aim of this study is highlighting the intrinsic link between risk and causality, examining diverse causality notions underlying distinct risk concepts, and outlining specific risk-emergent contexts and the epistemological bases for operational strategies. More concretely, in the following sections we will see how complex causality, reflecting complex systemic risk, can lead to uncertain scenarios, probabilistic causality addresses epistemic risk, and Bayesian models are fundamental for methodological risk, managing uncertainty, updating beliefs as new evidence emerges, and considering biases. These three dimensions converge for increasingly reliable and epistemologically grounded risk management.

2. *Risk analysis*

Risk analysis is a systematic process that involves identifying, understanding, assessing, monitoring, and mitigating all possible risks. Through

---

[1] They refer to situations or conditions that could give rise to risks in the future (i.e., uncertainties), but they have not been fully analyzed or assessed yet.

[2] A recognized, assessed, and documented risk; it's known and acknowledged, and usually has a plan or strategy in place to manage or mitigate its impact should it occur.

the systematic examination of various facts and factors, uncertainties, and the likelihood of adverse events (AEs) occurring, as well as their potential impact (Vose 2008), individuals or organizations can prioritize and control *identified risks*, developing strategies or actions to proactively mitigate or reduce their likelihood or impact by allocating resources effectively (ISO 31000 2018; Conrow 2003). The risk analysis paradigm includes three interrelated elements:

(i) *Risk detection and assessment* (science-based) is fundamental, providing support of decisions on managing risks. It consists of identifying potential hazards, analyzing the likelihood that each hazard *actually* causes harm, in order to gain a general understanding of the causal potential of a given stressor ("*Can it?*"), and assessing the significance of this potential in a particular population or context, considering e.g., levels of exposure, relevant conditions, vulnerability of the exposed system, etc., of the local context (Anjum, Rocca 2019). Insufficient evidence here implies inability/difficulty to make predictions ("*Will it?*").
(ii) *Risk management* (policy-based) is «simply what you do to prepare for the unexpected» (Iqbal 2019). Its aim is to address uncertainties and plan accordingly (EMA 2022) after risks are identified, ensuring that the benefits exceed the risks «by the greatest achievable margin for the individual patient and for the target population as a whole» (Sottosanti 2015).
(iii) *Risk communication and minimization* is the interactive exchange of info on the risk and action(s) to reduce it (Calvo, Zuñiga 2011).

Risks involve *known* safety issues, but also *unknown* potential outcomes and their probabilities. The former are AEs for which there is sufficient evidence of a link with the given exposure, i.e., established, well-documented threats with a high level of certainty, that can be identified in advance (typically through clinical trials, or long-term use of a particular product or process), making it possible to plan responses; while the latter are AEs where a link with the exposure is suspected but lacks confirmation (EMA, HMA 2017). As additional information emerges and understanding grows, these risks may either be confirmed and reclassified as *known* or may be deemed less likely or severe than initially perceived.

Based on the level of knowledge on a risk event's occurrence and its impact, it is possible to categorize risks as follows (Cleden 2009):

(i) two types of known (*identified*) risks:
  - *Known-knowns* (knowledge): risks which you are fully aware of and can plan in advance (controllable risks).

  - *Known-unknowns* (untapped knowledge): risks which you know exist, but can't accurately quantify their potential impact, or yet there is lack of convincing evidence for its concrete impact.

(ii) two types of *unexpected*, *unidentified risks*, which are unable to anticipate and describe:

  - *Unknown-knowns*: a hidden risk/element (*latent risk*[3]), which has not been grasped and could potentially be checked or assessed if a more in-depth analysis were made (avoidable risks). This type of risk is often associated with underlying vulnerabilities or weaknesses that might not be immediately apparent in normal operating conditions but could lead to problems if triggered by certain events or changes. These vulnerabilities can be the result of complex and often unexpected interactions between various components of a system (systemic risk context).
  - *Unknown–unknowns* (unfathomable uncertainty): possible risk events which can't be known in advance (unforeseeable, uncontrollable risks). They relate to emergent risks and are part of complex domain.

Despite the attempt to detect as many *unknown-knowns* as possible, turn them into *known-unknowns* and deal with them accordingly (Kulieasas 2017), it is impossible to identify *all* risks *in advance* for many reasons (Kim 2012; Hillson 2005), and *unidentified risks* remain as *unknown-unknowns* until they actually happen (Iqbal 2019).

In the healthcare field, e.g., the post marketing use of (bio)pharmaceuticals can be related to the occurrence of unknown adverse events (AEs) – including *latent risks* –, that may involve rare and/or serious health problems often resulting in hospitalization and/or permanent damage or death of the patient (Ilardo 2023). All this translates into a great need to detect and investigate *any* AE to predict (when predictable) and minimize risks. CA involves the investigation into the existence or not of a causal link between a given exposure and the subsequent adverse phenomenon (Bellavite 2020). Typically conducted as part of data monitoring activities, CA is crucial for decision-making, regulatory action, and public health policies (Shimabukuro *et al.* 2015), in that it allows a balancing of known benefits (e.g., reducing death and/or hospitalization, protecting people from serious

---

[3] This type of risk may be inherent in a system, process, or situation, but is hidden or dormant and its effects may only become evident (so it can be identified) under specific conditions or over time.

illnesses, etc.) with *possible but unverified risks* (WHO-HIS-EMP 2013). By evaluating the potential relationship between a specific exposure (e.g., drug, treatment, intervention) and observed adverse outcomes, CA aims at identifying *changes in risks* or *new risks* (AIFA 2012) to promptly enable accurate risk assessment and appropriate response to *new identified risks* minimizing both the negative effects to the individuals' and community health (CIOMS, WHO 2012; Al-Worafi 2020).

However, the analysis may sometimes fail to identify a causal link between an exposure and the adverse outcome when, in fact, such a link exists, i.e., *false negatives*. This means overlooking potential risks that should have been detected and might result in serious consequences such us inadequate preparedness, decision-making or interventions, delayed responses, or lack of preventive measures, thereby negatively impacting both individual and public health. Minimizing false negatives is crucial in the *risk detection and assessment* process (Ilardo 2023). The *complexity of systems* and uncertainties stemming from *the inherent randomness of threats* and our *incomplete understanding and measurement* of hazards, exposure, and vulnerability (UNDRR 2023) contribute to this challenge.

Causality and risk analysis are, therefore, interrelated elements in a cyclical and iterative process that addresses uncertainties and potential negative outcomes in various domains. The effectiveness of risk assessment, management and mitigation depends on accurate causal analysis. The foundational role of causality notions in any risk analysis is particularly relevant in governing complex systems, especially within the broad healthcare context (from drugs/vaccines to the entire ecosystem). Our focus therefore is on the interconnected facets of risk and causality more directly related to complexity, context dependence, systemic and interactive principles.

3. *The intertwining between risk's and causality's notions*

Causality in risk assessment is traditionally viewed as a *linear cause-and-effect relationship* that operate in a straightforward and predictable manner[4] (Hume 1739; Mill 1843; Lewis 1973, 1986), devoid of significant complexity or uncertainty (*linear risk*); i.e.: «a causal-effect relationship between causal factor and disease without factor intervening in processes» (WHO 2019). This perspective works in scenarios with outcomes *directly* traceable

---

[4] The causal influence of one event on another is *direct* (Spohn 1990).

to *identifiable* causes, like simple systems or controlled environments, informing effective interventions and enabling *more certain* (or *stronger*) predictions (Anjum, Rocca 2019) – i.e., *predictable outcomes* based on *identified* cause-and-effect relationships (*known risk*).

3.1. *Complex causality and uncertainty*

However, the real world is rarely so "simple". Causal structures are *complex* and *variable* networks of dependencies (Mackie 1974; Rothman 1976; Rothman, Greenland 2005; Parascandola, Weed 2001) – this is particularly true in so-called "soft-sciences", like sociology, economics, medicine. Effects can ontologically depend on multiple causes (antecedent, concomitant or subsequent), or risk factors, of various kinds (exogenous and endogenous), and even different mechanisms of causality (Lebiu *et al.* 2017). Causal factors are conceptualized as system' elements that interact with each other and with the system's environment (Renn *et al*. 2022) in complex way either precipitating the AE or by acting as cofactors[5] (Bellavite 2020; Rothman 2012), and that vary depending on the context (context-sensitivity[6], individual variability and uniqueness) (Mumford, Anjum 2011) – this underscores the significance of local, contextual knowledge.

According to systemic and interactionist view within a system it is *impossible* to hypothesize a *certain and linear causality* between variables, since *all* the elements of the system *influence* each other (Zappulla 2019), and different types of causal influence exist (e.g., indirect, mediating, modifying, moderating, hasteners, delayers) (Ilardo 2023). Causal relationships are influenced by various intervening factors (some *known*, others *unknown*) – including *mediators*[7] and (genetic, environmental, stochastic, etc.) *modifiers* (Koeske 1992; Kramer 1988; Susser 1973) – that contribute to poorly understood emergent effects (Pearl 2009) (*potential risk*) operating through intricate, often *non-linear,* interactions [(Mackie 1974; Cartwright, McMullin 1984; Woodward 2003; Bertolaso, Buzzoni 2017)]. Mechanisms are com-

---

[5] Co-causes can act as difference-makers or be involved in a chain of reactions wherein interactions among causes lead to the effect.

[6] Context sensitivity refers to the joint interaction of diverse causes in determining an effect and modulating its intensity (Osimani 2020). The cumulative or summative effect of multiple causes is considered (X+Z+Y→E), whereby a greater number of causal factors increases the intensity of the outcome.

[7] The influence of the first cause on the final effect of a concatenation is mediated by other events in between (intermediate event) (Spohn 1990).

plex and contextual phenomena, and causation is potential (Rocca, Anjum 2020b): e.g., a predisposing factor may cause the effect with the intervention of another factor that may accelerate or reinforce the effect or trigger it (Rocca *et al.* 2020).

Non-linear causality, explaining inherent events' interconnectedness through micro-macro dynamic interactions, introduces indeterminism (i.e., events may occur without *a priori known* cause), leading to uncertainty and unpredictability[8] in outcomes (Simon 1992; Lucas *et al.* 2018).

Even if a causal set of factors sufficient for the effect E is identified and the dynamical laws of the system are known (determinism), one cannot predict *with certainty* whether, e.g., a smoker *will* develop lung cancer. Doing it would mean that in 100% of cases when you have the causal set you have E, implying exact reproducibility and predictability of E, and minimization/absence/explanation of variability[9]. Nevertheless, many events are not precisely predictable, and their variability cannot be reduced/explained: i.e., probabilistic events. In medicine, e.g., diseases typically stem from multiple sets of causes which do *not* invariably lead to a given effect. In some situations, one causal factor may play a prominent role, eclipsing other contributing factors and giving the impression of a deterministic event (e.g., germs in infectious diseases, poisons in intoxications, etc.) (Ilardo 2023). Conversely, in other cases, the disease's onset appears to be more probabilistic in nature (e.g., tumors, autoimmune diseases, etc.), often characterized by randomness or chance. Here causes may *raise* (or *change*) *the probability* of their effect (Reiss 2015; Cartwright 1979; Eells 1991; Lagiou *et al.* 2005; Parascandola, Weed 2001) and causality is a *probable conjunction* (Suppes 1970).

In contexts where causation analysis is highly complex and characterized by strong uncertainty one can only attempt to assess the extent to which each factor may have contributed to (increased the probability of) the effect (Ilardo 2023). Since there are several possible causalities rather than just one, each should be evaluated in the context provided by probability (Edwards 2012).

---

[8] Even simple relationships may exhibit high uncertainty if the knowledge base is lacking, or effects may be indeterminate due to stochastic functional relationships (Neyman 1960; Renn *et al.* 2022).

[9] In experimental settings, variability can be reduced (sometimes almost to zero) by controlling the experimental conditions. However, for natural events where conditions can be investigated but not controlled, variability can only be explained (e.g., Newton's theory accurately predicting and explaining planetary orbits).

Complexity involves the challenge of identifying and quantifying causal links among many elements due to interactive effects (synergisms and antagonisms), positive and negative feedback loops (where the consequences of an event can amplify and cascade through the system)[10], short/long delay periods between cause and effect, interindividual variations, intervening variables, etc. (Renn *et al.* 2022). It manifests in different forms (a) *organized,* (b) *disorganized* (Bertolaso 2022) and (c) *genuine complexity* (Rocca, Anjum 2020a). They respectively refer to complex systems that (a) exhibit a degree of order and can be decomposed into manageable subsystems with identifiable patterns, allowing for some level of predictability; (b) lack clear patterns, making them harder to understand or predict (randomness or chaos may be more apparent); (c) are characterized by emergent novel properties (not easily deducible from the individual components' properties), adaptivity (adjusting to changes in system's environment), evolution at varying speeds and over different time frames, and inherent intricacy from non-linear interactions, where «the parts of a whole change each other» (Rocca, Anjum 2020a) and small changes can yield disproportionately large effects.

These causal complexities, central in many risk situations, reflects *systemic risk* (Schweizer 2021; OECD 2003). Ontologically speaking, this type of risk exhibits (Renn *et al.* 2022): (i) high complexity and dynamics (Lucas 2020), (ii) strong and multiple uncertainties, (iii) vulnerability to external shocks[11]; (iv) the potential for widespread and cascading effects across time and space (Smith, Fischbacher 2009; Florin 2018; Aven, Renn 2019), altering the system' equilibrium. Acceleration of spatial-temporal variability and changes in cause-and-effect interrelationships (Forzieri *et al.* 2017; IRGC 2018), coupled with the ambiguous or even unknown nature and magnitude of resulting effects (Lucas *et al.* 2018), enhance uncertainties and further affect the predictability of future events (De Bruijne *et al.* 2010).

Uncertainty here arises from inherent features of the system, variability due to stochasticity, but also from ignorance due to incomplete or wrong knowledge and epistemic indeterminacy (Howick 2011; Parascandola 2011; van Asselt 2000)] – systemic risk turns epistemic. In complex interconnected systems, there might be hidden, underlying susceptibilities

---

[10] Feedback loops play a crucial role in understanding the dynamics of complex systems, influencing how they respond to changes and maintain stability or undergo transformation.

[11] They can trigger widespread disruptions. In the context of ecosystems, e.g., an invasive species or a sudden change in climate can pose systemic risks to biodiversity.

(*latent risks: unknown-knowns*) that contribute to *systemic risk* if triggered, e.g., amplifying/accelerating the impact of systemic failures (Rocca *et al.* 2020). A more in-depth analysis of the mechanisms underlying the observed effects, interactions, and complex systemic dynamics at work is needed (Hulme, Finch 2015; Russo, Williamson 2007) to obtain a detailed causal understanding of *why* and *how* something might or might not happen (Salmon 1998; Rocca, Anjum 2020b) and to help in establishing whether the link is causal or not. This serves not only to form causal hypotheses about the cause of harm, but also for developing appropriate solution and safety evaluation (Gillies 2018). Not all mechanisms, however, are easy to identify, and even if they were, many will probably *never* be *fully* known or will only be *partially* known. There is often absent/limited/incomplete/insufficient knowledge/data about: how different components influence each other, how certain components may interact under specific conditions, emerging dynamics, changes in time and space of conditions, feedback mechanisms, potential vulnerabilities within the system or the ways in which failures can propagate.

The fact that the knowledge of the mechanisms of a phenomenon may be at any given time incomplete and also wrong (Howick 2011), has led to emphasize population-based statistical evidence over mechanistic knowledge. This evidence provides information on the likelihood or chance of an event occurring, expressing causal relationships in terms of probabilities, paving the way for predictions based on statistical uncertainties.

3.2. *Probabilistic causality and* epistemic risk

Probabilistic causality involves the use of probability to represent uncertain causal relationships, estimating event probabilities based on available information – i.e., assessing and quantifying[12] potential risk (harmful effects in a given population). Epidemiological (experimental, observational) studies aim at denying or confirming and quantifying the signals in terms of risk (Ilardo 2023) [e.g., «smoking causes lung cancer with such-and-such probabilities»[13] (Dragulinescu 2012)]. The focus is on *potential* causal propositions for populations: *"Can It?"* (general knowledge).

Statistical analysis uncovers empirical associations by examining depen-

---

[12] E.g., quantitative risk assessment (QRA) (Duarte *et al.* 2019; Harwell *et al.* 2012).

[13] A specific event is accompanied by another event in a high percentage of cases: the event is only probable, though to a considerable extent (Rossi 2000).

dences between variables of a population or a sample in which the degree of the AE (e.g., pathology) in those with specific exposure (e.g., medicine's intake) is higher or lower than the rate of AE among those without exposure (ECDC 2018; Mota, Kuchenbecker 2017). The difference in risk expresses the probability of the risk of an AE caused by the exposure. Measuring events' probability allows for a refined estimated of hazard frequencies and damages assessment, and so for better evidence to inform decision-making helping in selecting the more appropriate strategies for different scenarios[14] (UNDRR 2023).

In biomedical and social research, causal knowledge based on this evidence is central to scientific inquiry. It allows to predict[15] an event of the type that has occurred with a *high degree of certainty* or *probability* (Hart, Honoré 1985; Summerer 2013; Pearl 2000, 2009; Woodward 2003) – i.e., *strong* scientific evidence. Evidence Based Medicine (EBM) relies on statistical and population-based evidence generated from large clinical studies, mainly RCTs (Howick 2011), because thanks to their experimental design, and if well conducted, they are best at isolating a causal factor from potentially confounding factors and seeing if it makes a statistical difference in the outcome (Anjum *et al.* 2020), interpreting results in terms of its causal impact on the outcome. Only those factors that increase the probability of their effects on *average* in a causal homogeneous population[16] (Lagiou *et al.* 2005) are causes (Dupré 1984). However, there are inherent limitations and challenges in these studies (Papanikolaou *et al.* 2006; Vandenbroucke 2008).

These methods, also referred as clinchers (Cartwright 2007b), are elitist since they «value evidence for the degree to which they exclude random and systematic error» and deductively force their conclusions accepting/rejecting the causal hypothesis under investigation based on statistical evidence (i.e., *hypothesis testing*) (Osimani 2020). An intended (and therefore *known*) causal relationship is tested to verify its validity (benefit assessment) – focus on false positives. However, this approach is deemed epistemologically and methodologically flawed when evaluating harms, where you observe and

---

[14] E.g., risk reduction in the case of extended risks, risk transfer in the case of higher impact (but less likely) events.

[15] "*Will it?*" refers to the frequency with which a given exposure causes a specific AE: i.e., the percentage of exposed who will experience the AE as a result of the exposure (quantification).

[16] A causally homogeneous population is when there is no variation in the causes influencing a given outcome within that population: e.g., if sex is a causally relevant factor, a population is causally homogeneous if every member is exclusively female or exclusively male, etc. (Reiss 2015).

gather evidence, which you are called on to explain in some way (Osimani 2014), rather than starting with a certain hypothesis and then gather evidence to test it. In case of AEs we are dealing with risk detection, hence with the problem of *latent* risks (yet *unknown* and unthought by the scientific community phenomena), where the focus is on false negatives (i.e., on the problem of failing to recognize causality, when in fact there is) (Hansson, Rudén 2008).

Statistical methods, despite presenting objective standards (like P-values, confidence intervals and relative risks), may create a false sense of complete objectivity in assessing causal links. However, it is nearly impossible to confidently reject a causal relationship on their basis, as even the largest epidemiological studies lack adequate statistical power to detect extremely rare (and/or serious) or delayed adverse outcomes (Autret-Leca *et al.* 2006; Ilardo 2023).

Issues such as selection bias, diversity of non-randomized groups further complicate low-incidence AE cases (Bellavite 2020). In addition, while controlled conditions increase the reliability of the experimental results and the confidence that the observed outcome is due to the tested intervention, this limits external validity (Anjum *et al.* 2020), as the studied population may differ significantly from the real-world treated population.

Epidemiological evidence indicates increased AE risk among some people in the population with specific characteristics (Counil 2021), but the risk is only a measure of how much individual AE probability increases (e.g., in exposed compared to unexposed), conditional on the factor's exposure. This evidence tells us, e.g., that a toxin *can* produce an injury (statistical contribution) but is unable to tell us that the exposure to that toxin *actually* caused that specific injury in that specific situation (Parascandola 1998; Casali 2010). Other substances are also known to being able to cause that injury, and some people exposed to same toxin may develop the injury, while others not. As Reiss (2016) underlines, whether a factor can be considered cause depends on the *actual* distribution of factors in a population: a treatment that is effective on average can be harmful to some. If the effect is different, it may mean that either something was different in the cause or in the background conditions, so if two (or more) patients with the same disease get different effects from the same treatment, there must be some *causal relevant difference* between them (Rocca, Anjum 2020a). These considerations refer to the heterogeneity of various subgroups in the population, more specifically to multifactoriality, individual uniqueness, variability, and context-sensitivity.

Real-life causation is not a linear process which can be evaluated epidemiologically. Causes are complex, intrinsic, tendential and context-sensitive phenomena (Rocca *et al.* 2020). A tendency that is *statistically weak*, like, e.g., the tendency of oral contraception to produce thrombosis, in some individuals, *could be very strong and in any case*, however it cannot manifest itself alone or in isolation: causal production is a matter of complex interaction of multiple dispositions, many of which are represented by the background conditions (*dispositionalism*, Rocca, Anjum 2020b). Focusing on a single cause, intervention, or stressor, when making predictions about the outcome and ignoring or losing relevant information about the unique local context (Cartwright, Hardie 2012), statistical approaches fail to uncover most of the causally relevant factors of the causal interaction (Anjum, Rocca 2019; Anjum *et al.* 2020). Causation may be due to not fully understood or controlled factors, and the outcome may follow a stochastic pattern (Kóbor *et al.* 2023).

As Edwards (2018) underlined, the fact that causality is high context-dependent, «contrasts with the isolated factor of conventional science where we reduce a complex multidimensional issue to a one-dimensional form» – see also (Bertolaso 2022). The controlled setting while aiming to isolate the impact of the intervention and minimize confounding variables, *simplify the complexity of the real-world contexts* leading to a narrow perspective, not capturing the broader context of factors influencing outcomes and overlooking environmental stochasticity[17] (Joffe *et al.* 2012). All this means missing relevant issues when it comes to causal indications regarding AEs, failing to detect existing *but yet unknown* phenomena: *latent risk* (*unknown-knowns*). Since most AEs are unknown, studies, even observational, cannot be designed to identify the connection of these effects with the investigated exposure in a statistically significant way.

Moreover, as we have seen in the previous section risks within highly complex and connected systems (Smith, Fischbacher 2009) are characterized by (i) cross-sectoral impact leading to multiple ripple effects (IRGC 2018) (ii) highly interconnectedness and intertwines resulting in complex causal structures, (iii) often non-linear cause–effect relationships resulting in unexpected outcomes, often featuring unknown tipping points or parts (Scheffer 2010) (iv) stochastic effect structure[18]. All this is challenging or

---

[17] Moreover, it must be said that the isolation or control of the causal factor as much as possible from its complexity to see what it does on its own, is not always be practically possible (Anjum, Rocca 2019).

[18] I.e., the probabilistic or random nature of the relationships and patterns within a system or process.

impossible to characterize using e.g., statistical confidence intervals (commonly used in epidemiology) (Renn *et al.* 2022). In such a context we are often dealing with low-probability, high-consequence events (*unknown-unknowns*) (Taleb 2007), difficult to be known in advance, making it crucial to go beyond statistical correlation by attempting to understand the mechanisms and dependencies that give rise to observed data.

As Joffe *et al.* (2012) stated, all the above-mentioned different sources of uncertainty:

> […] can have an impact on various steps of the risk assessment paradigm […] resulting in hazards that are not recognized, hazards that are incorrectly identified, or inaccurate dose-response characterizations that may lead to over- or underestimation of "safe" exposure levels.

The possibility of forming errors and/or false beliefs or conclusions (*false positives* or *false negatives*) from statistical evidence characterizes *epistemic risk* (Biddle, Kukla 2017). The goal here consists in reducing (false) negatives, which naturally trades off with the goal of reducing (false) positives, while embracing uncertainty as an inherent feature of complex systems stemming from both *the inherent randomness of threats* and their *incomplete understanding and quantification*, influencing decision-making. If relevant probabilities are unavailable or only partially available, we are in the scenario of decision "under uncertainty".

Firstly, faced with a potentially high risk, to which, due to inherently limited knowledge and/or the few confusing insufficient/inconclusive/uncertain data available, it is difficult to give more precise contours, «precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically» to protect human health or the environment» [(Wingspread Conference on the Precautionary Principle 1998) – *precautionary principle*. The probability of causal link here can be as low as the expected damage is high with respect to the estimated benefit: i.e., *adaptive response* to risk monitoring (Osimani, Ilardo 2022; Ilardo 2023). This norm of expected loss minimization allows uncertain evidence (i.e., risk whose causal link with the source of danger is uncertain) to be included in the risk/benefit assessment[19], underpinning risk management and prevention measures (Osimani 2013).

---

[19] Risk-benefit assessment is based on a comparative weighing of therapeutic importance and efficacy on the one hand, and of the severity and frequency of risk on the other (Osimani 2010).

When there is no previous knowledge on the fact under examination (little or no available data on it), applying probabilistic reasoning around the causal link in qualitatively terms according to logical probability can open up many possibilities – high degree of logical probability.

3.3. Towards integrated approaches: bayesian models and methodological risk

To address the inherent limitations in the knowledge of complex systems, characterized by numerous components and potential interactions leading to unexpected changes and unpredictability (SEP 2022; Kóbor *et al.* 2023), a shift towards an integrated perspective (Laniak *et al.* 2013; Sexton 2015), that tackles causal complexity and interdependencies, acknowledging synergistic, antagonistic, and nonlinear interactions (Callahan, Sexton 2007; Williams *et al.* 2012), instead of isolating individual events or factors from their intricate interactions, is key. Essential info on causal interaction often stems from basic science (molecular studies; in vitro or in silico tests) or comprehensive case series, that may significantly contribute to identifying specific subclasses where the treatment's effect varies to a greater or lesser extent (Osimani 2020), rather than from experimental studies alone. Thus, unlike focusing solely on population-level risks this approach must also examine real-world case studies, involving individuals, communities, and stakeholders as valuable sources of knowledge (Gallagher *et al.* 2015) – see (Anjum, Rocca 2019). Along experimental evidence a variety of different types of evidence collected in specific contexts[20] must be gathered (evidential pluralism) (Landes *et al.* 2018) and then used for risk assessments and predictions in various scenarios. An example of such a framework that sought to overcome the limitations of conventional statistical approaches is the Comprehensive Risk Assessment (CRA) (U.S.EPA 2003), reported by Anjum and Rocca (2019).

Additional strategies may include:

(i) Modeling and simulation of the system or its networks to explore and predict possible future risk situations, including extreme and unexpected events (Giannakis, Louis 2011). This process entails «capturing experimentally tested and validated cause-effect relationships

---

[20] E.g., experimental animals (toxicology), exposed individuals (pharmacovigilance), communities (epidemiology), populations (experimental studies), ecosystems (ecology) (Anjum, Rocca 2019).

within a complex web of causes and effects» (analytical realist perspective) and «anticipating human responses to unprecedented events for which empirical data are insufficient or lacking» (analytical constructivist approach) (Renn *et al.* 2022).

(ii) Creation of interconnected model networks derived from different disciplines perspectives and methodologies (Schanze *et al.* 2012) to help in effectively capturing different future developments in complex system-environment interactions: «the interplay between diverse disciplinary perspectives on risk can generate new understandings that may have a relevance to various types of hazards along with their prevention and management» (Smith, Fischbacher 2009) – see also (Chandler 2019).

(iii) Implementation of monitoring systems and early warning mechanisms to detect unusual patterns, outliers, or signals indicative of emerging unexpected risks. This involves leveraging technology and data analytics to identify anomalies.

(iv) Building/enhancing *resilience* or *robustness* of the risk-absorbing system, making systems, processes, and structures more *flexible* and *adaptive* to withstand unexpected shocks (Allen *et al.* 2016; Hollnagel *et al.* 2015; Finkel 2011), instead of solely attempting to identify and prevent risk-generating agents (Renn *et al.* 2022).

In situations of epistemic uncertainty, Bayesian networks (probabilistic graphical models) and methodology can facilitate scenario analysis and simulation accounting for complex causal relationships in terms of probability (Hitchcock 2016; Pearl 2009). The former help in representing and analyzing complex relationships and dependencies among a set of variables in a system, considering the context in a unitary way, where individual, relational and environmental variables form an *integrated and dynamic system*, made up of inseparable elements that influence each other (Zappulla 2019), and trying to understand the potential impacts and cascading effects of *unknown-unknowns*. The latter help in dealing with uncertainties in the available data or knowledge, updating beliefs (or probabilities) based on new evidence or information, and accounting for potential biases (Pearl 2000) [It can help in reclassify *unknown-unknowns* and/or *unknown-knowns* into *known risks*].

Bayesian causality is pivotal for *methodological risk* since it allows for a *dynamic* and *iterative* approach to modeling by incorporating prior beliefs or knowledge about a system as new data emerge. Being based on the constant revision of causally justified assumptions (Cartwright 2007b), Bayesian methods prove *flexible* (in terms of the kind of evidence that can be considered) and valuable tools for risk assessment. They are *flexible* enough to incorporate new possibly conflicting evidence in the inferential framework, without necessary eliminating old beliefs, and allowing to use evidence vouchers, useful for decisions in the field of uncertainty (Ilardo 2023). This means that they do not require conclusive evidence but allow evidence that "speaks" of a causal relationship, and that can be *combined* with evidence of different kinds[21] from other methods to suggest or support a conclusion of causality more or less strongly (Osimani 2020; Osimani, Mignini 2015). *Vouchers methods* seek to offer a way to evaluate the *degree of plausibility* of a given hypothesis given a set of data (i.e., graded judgment) and, if feasible, measure it probabilistically (Cartwright 2007a, 2007b) – inductive Bayesian reasoning. Integrating info from diverse safety signal sources would allow to achieve accurate CA, avoiding a rise in the likelihood of false negatives (Osimani 2014).

A valuable and useful implementation of a Bayesian approach in medicine and pharmacology is exemplified by E-Synthesis: a methodological tool for aggregating many types of evidence (e.g., cell-data, clinical-data, epidemiological studies, etc.) to probabilistically assess causality between medicines and AEs. It involves a Bayesian epistemic network that probabilistically formalizes scientific inference and can be tailored to «various theoretical stances on causality (counterfactual vs. process theories vs. regularity vs. inferentialist theories of causality)» (Osimani 2020).

4. *Conclusions*

Causality notions significantly constrain risk management and assessment processes. Acknowledging the limitations of deterministic thinking and of linear cause-and-effect brings to a different epistemological perspective in order to develop operational strategies that align with the intricacies and inherent uncertainties of each unique complex risk landscape. As shown, any methodology that (implicitly or explicitly) embraces a narrow notion of causality tends to restrict the range of cases in which phenomena are deemed causal, excluding events and phenomena not aligning with its

---

[21] Vouchers appeal to the *Principle of Total Evidence*, as «an essential desideratum in non-monotonic reasoning, as opposed to the hypothetico-deductive paradigm» (Osimani 2020).

predefined criteria, thereby leading to *increase false negatives*. This means the non-identification of *potential risks* that should have been detected, with consequent inadequate preparedness, decision-making or interventions.

From a methodological standpoint, the concept of *cause* underpinning CA procedures must be *flexible* and *wide* enough to reliably enable the accurate detection of all causal phenomena and concurrently to minimize failures to identify such phenomena when they are present. In this regard, voucher and evidential pluralistic methods, advocating for a diversity of ways of knowing to better grasp the complexities of risk in diverse settings, are particularly useful in risk detection, supporting a decrease in *false negatives,* thus enhancing the accuracy and reliability of the analysis processes.

Moreover, a multidimensional and probabilistic-based approach ensures a more nuanced, inclusive, and dynamic risk management paradigm, facilitating the development and adoption of adaptive risk management strategies that are *flexible*, *resilient*, and *responsive* to changing circumstances, allowing for iterative adjustments based on ongoing assessments and effective solutions – in such a process humans are essential asset contributing to the flexibility and resilience of systems. This necessitates specific lines of action including embracing uncertainty as an inherent feature of complex systems, influencing decision-making strategies that can adapt to dynamic and unpredictable conditions.

Finally, given the dynamic nature of emerging hazards and the safety management principle of keeping the *adaptive capacity* to respond effectively to unexpected outcomes, moving away from old standard notions of causation and embrace newer perspective(s) is necessary. Methodologically, addressing complex risks effectively requires a shift towards a perspective that adopts: evidential pluralism, integrating all available evidence about specific settings and contexts into causal inferences, and inductive reasoning (e.g., Bayesian methods of hypothesis confirmation) instead of the hypothetico-deductive inferential paradigm underlying current practices (EBM).

All this entails embracing a multidisciplinary, *dynamic* approach focused on scientific and investigative depth, using all available tools for collecting, analyzing, and synthetizing data, including *artificial intelligence, machine learning*, *knowledge retrieval* techniques and systemic biomedical studies. This may be of great help in accurately assessing emergent risks and is particularly important for dealing with low-probability, high-consequence events (also referred to "black swan" events or unforeseeable risks, i.e., *unknown-unknowns*) and contextualized within highly complex and connected systems.

Complex causality and uncertainty, probabilistic causality and epistemic risk, Bayesian models and methodological risk, represent three dimensions to be considered for an increasingly reliable and epistemologically grounded risk management.

Author Contributions: The authors equally contributed to the paper's structure and arguments. M.L.I. performed the analysis in sections 2 and 3 and wrote them. M.B. contributed with critical reviews of the previous versions and with sections 1 and 4.

References

AIFA (2012), *La nuova legislazione di farmacovigilanza*, URL = <https://www.aifa.gov.it/-/la-nuova-legislazione-di-farmacovigilanza>.

Al-Worafi, Y.M. (2020), *Pharmacovigilance*, in Id., *Drug Safety in Developing Countries: Achievements and Challenges*, Academic Press Elsevier Inc, Cambridge (MA), pp. 34-35.

Allen, C.R., Garmenstani, A.S., Sundstrom, S.,, Angeler, D.G. (2016), *Ecological resilience*, in M.-V. Florin, I. Linkov (eds.), *IRGC resource guide on resilience*, EPFL, Lausanne, vol. 1. https://doi.org/10.5075/epfl-irgc-228206

Anjum, R.L., Rocca, E. (2019), *From ideal to real risk: philosophy of causation meets risk analysis*, in «Risk Analysis», 39, pp. 729-740. https://doi.org/10.1111/risa.13187

Anjum, R.L., Copeland, S., Rocca, E. (2020), *Rethinking Causality, Complexity and Evidence for the Unique Patient: A CauseHealth Resource for Healthcare Professionals and the Clinical Encounter*, Springer Nature, Cham. https://doi.org/10.1007/978-3-030-41239-5

Autret-Leca, E., Bensouda-Grimaldi, L., Jonville-Béra, A.P., Beau-Salinas, F. (2006), *Pharmacovigilance of vaccines*, in «Archives de Pediatrie: Organe Officiel de La Societe Francaise de Pediatrie», 13 (2), pp. 175-180. https://doi.org/10.1016/J.ARCPED.2005.10.020

Aven, T. (2016), *Risk assessment and risk management: Review of recent advances on their foundation*, in «European Journal of Operational Research», 253 (1), pp. 1-13. https://doi.org/10.1016/j.ejor.2015.12.023

Aven, T., Renn, O. (2019), *Some foundational issues related to risk governance and different types of risks*, in «Journal of Risk Research», 1, pp. 1-14. https://doi.org/10.1080/13669877.2019.1569

Aven, T., Zio, E. (2014), *Foundational issues in risk assessment and risk management*, in «Risk Analysis», 34 (7), pp. 1164-1172. https://doi.org/10.1111/risa.12132

Beck, U. (1992), *Risk Society. Towards a New Modernity*, translated by M. Ritter, Sage, London.

Bellavite, P. (2020), *Causality assessment of adverse events following immunization: the problem of multifactorial pathology* [version 2; peer review: 3 approved, 1 approved with reservations], in «F1000Research», 9 (170). https://doi.org/10.12688/f1000research.22600.1

Bertolaso, M. (2022), *Understanding complexity in life sciences*, in V. Ingegnoli, F. Lombardo, G. La Torre (eds.), *Environmental Alteration Leads to Human Disease: A Planetary Health Approach*, Springer International Publishing, Cham, pp. 1-13. https://doi.org/10.1007/978-3-030-83160-8_1

Bertolaso, M., Buzzoni, M. (2017), *Causality and Levels of Explanation in Biology*, in M. Paolini Paoletti, F. Orilia (eds.), *Philosophical and Scientific Perspectives on Downward Causation, Part II - Downward Causation and the Sciences*, Routledge, New York, pp. 164-179. https://doi.org/10.4324/9781315638577

Biddle, J.B., Kukla, R. (2017), *The Geography of Epistemic Risk*, in K.C. Elliott, T. Richards (eds.), *Exploring Inductive Risk: Case Studies of Values in Science*, Oxford University Press, New York, pp. 215-237.

Callahan, M.A., Sexton, K. (2007), *If cumulative risk assessment is the answer, what is the question?*, in «Environmental Health Perspectives», 115 (5), pp. 799-806. https://doi.org/10.1289/ehp.9330

Calvo, B., Zuñiga, L. (2011), *Risk Management Plan and Pharmacovigilance System. Biopharmaceuticals: Biosimilars*, in G. Nota (eds.), *Risk Management Trends*, InTech, London, p. 13. https://doi.org/10.5772/16246

Cartwright, N. (1979), *Causal Laws and Effective Strategies*, in «Noûs», 13 (4), p. 437. https://doi.org/10.2307/2215337

Cartwright, N. (2007a), *Hunting Causes and Using Them: Approaches in Philosophy and Economics*, in «Journal of Economic Literature» (Issue January), Cambridge University Press, Cambridge.

Cartwright, N. (2007b), *Are RCTs the Gold Standard?*, in «BioSocieties», 2 (1), pp. 11-20. https://doi.org/10.1017/S1745855207005029

Cartwright, N., Hardie, J. (2012), *Evidence-based policy: A practical guide to doing it better*, Oxford Academic, New York.

Cartwright, N., McMullin, E. (1984), *How the Laws of Physics Lie*, in «American Journal of Physics», 52, pp. 474-476. https://doi.org/10.1119/1.13641

Casali, M. (2010), *L'accertamento del nesso di causalità*, URL = <https://www.responsabilitasanitaria.it/eventi_passati/2010-11-03/pdf/CASALI-L'accertamento_del_nesso_di_causalita.pdf.>.

Chandler, R.E. (2019), *Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events*, in «BMJ», 365. https://doi.org/10.1136/BMJ.L2268

CIOMS, WHO (2012), *Definition and Application of Terms for Vaccine Pharmacovigilance*, URL = <https://cioms.ch/wp-content/uploads/2017/01/report_working_group_on_vaccine_LR.pdf>.

Cleden, D. (2009), *Managing Project Uncertainty* (1st ed.), Routledge, New York. https://doi.org/10.4324/9781315249896

Conrow, E.H. (2003), *Effective Risk Management: Some Keys to Success*, AIAA, Reston (Vancouver).

Counil, E. (2021), *Contribution of causal factors to disease burden: how to interpret attributable fractions*, in «Breathe (Sheffield, England)», 17 (4), 210086. https://doi.org/10.1183/20734735.0086-2021

De Bruijne, M., Boin, A., Van Eeten, M. (2010), *Resilience: Exploring the concept and its meanings*, in L.K. Comfort, A. Boin, C.C. Demchak (eds.), *Designing resilience: Preparing for extreme events*, University of Pittsburgh Press, Pittsburgh (PA), pp. 13-32.

Dragulinescu, S. (2012), *On Anti Humeanism and Medical Singular Causation*, in «Acta Analytica», 27 (3), pp. 265-292. https://doi.org/10.1007/S12136-011-0141-1/FIGURES/6

Duarte, H.O., Droguett, E.L., Moura, M.C., Siqueira, P.G.S.C., De Lira, J.C. Jr. (2019), *A novel quantitative ecological and microbial risk assessment methodology: Theory and* practice, in «Human and Ecological Risk Assessment: An International Journal», 26 (6), pp. 1622-1645. https://doi.org/10.1080/10807039.2019.1596736

Dupré, J. (1984), *Probabilistic Causality Emancipated*, in «Midwest Studies in Philosophy», 9, pp. 169-175. https://doi.org/10.1111/j.1475-4975.1984.tb00058.x

ECDC (2018), *Training of Trainers in Epidemiology of Vaccine Preventable Diseases*, URL = <https://slideplayer.com/slide/14708374/>.

Edwards, I.R. (2012), *Considerations on causality in pharmacovigilance*, in «International Journal of Risk & Safety in Medicine», 24 (1), pp. 41-54. https://doi.org/10.3233/JRS-2012-0552

Edwards, I.R. (2018), *Living with complexity and big data*, in «Uppsala Reports», 78, pp. 28-29, URL = <https://view.publitas.com/uppsala-monitoring-centre/uppsala-reports-78/page/28-29>.

Eells, E. (1991), *Probabilistic Causality* (vol. 1), Cambridge University Press, Cambridge. https://doi.org/10.1017/CBO9780511570667

EMA (2022), *Risk management*, URL = <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management>.

EMA, HMA (2017), *Guideline on good pharmacovigilance practices (GVP), Annex I, Definitions (Rev 4)*, URL = <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf>.

Finkel, M. (2011), *On Flexibility: Recovery from Technological and Doctrinal Surprise on the Battlefield*, Stanford University Press, Stanford (CA).

Florin, M.V. (2018), *Resilience in IRGC's recommendations for risk governance*, in «Resource guide on resilience», EPFL, Lausanne, International Risk Governance Center, URL = <https://irgc.org/wp-content/uploads/2018/09/Florin-Resilience-in-IRGCs-Recommendations-for-Risk-Governance-1.pdf>.

Forzieri, G., Cescatti, A., Silva, F.B., Feyen, L. (2017), *Increasing risk over time of weather-related hazards to the European population: A data-driven prognostic study*, in «Lancet Planetary Health», 1 (5), pp. e200-e208. https://doi.org/10.1016/S2542-5196(17)30082-7

Gallagher, S.S., Rice, G.E., Scarano, L.J., Teuschler, L.K., Bollweg, G., Martin, L. (2015), *Cumulative risk assessment lessons learned: A review of case studies and issue papers*, in «Chemosphere», 120, pp. 697-705. https://doi.org/10.1016/j.chemosphere.2014.10.030

Giannakis, M., Louis, M. (2011), *A multi-agent based framework for supply chain risk management*, in «Journal of Purchasing and Supply Management», 17 (1), pp. 23-31. https://doi.org/10.1016/j.pursup.2010.05.001

Gianti, D., Monateri, P.G., Balestrieri, M. (2016), *Causazione e giustificazione del danno* (vol. 3), G. Giappichelli Editore, Torino.

Gillies, D. (2018), *Causality, probability, and medicine* (1st ed.), Routledge, Abingdon, pp. 1-300. https://doi.org/10.4324/9781315735542

Hansson, S.O., Rudén, C. (2008), *A risk-neutral default for chemical risk management*, in «American Journal of Industrial Medicine», 51 (12), pp. 964-967. https://doi.org/10.1002/AJIM.20636

Hart, H.L.A., Honoré, T. (1985), *Causation in the law* (2nd Eds.), Oxford University Press, Oxford.

Harwell, M.A., Gentile, J.H., Parker, K.R., Murphy, S.M., Day, R.H., Bence, A.E., Neff, J.M., Wiens, J.A. (2012), *Quantitative assessment of current risks to harlequin ducks in Prince William Sound, Alaska, from the Exxon Valdez oil Spill*, in «Human and Ecological Risk Assessment:HERA», 18 (2), pp. 261-328. https://doi.org/10.1080/10807039.2012.650582

Hillson, D. (2005), *Why Risks Turn into Surprises*, in «Risk Doctor Briefings [Electronic Version]», n. 16, URL = <http://www.risk-doctor.com/pdf-briefings/risk-doctor16e.pdf>.

Hitchcock, C. (2016), *Probabilistic Causation*, in A. Hájek, C. Hitchcock (eds.), *The Oxford Handbook of Probability and Philosophy*, Oxford University Press, Oxford, pp. 815-832.

Hollnagel, E., Wears, R.L., Braithwaite, J. (2015), *From Safety-I to Safety-II: a white paper*, in «The resilient health care net», published simultaneously by the University of Southern Denmark, University of Florida, USA, and Macquarie University, Australia, URL = <https://www.england.nhs.uk/signuptosafety/wp-content/uploads/sites/16/2015/10/safety-1-safety-2-whte-papr.pdf>.

Howick, J.H. (2011), *The philosophy of evidence-based medicine*, John Wiley & Sons, Chichester.

Hulme, A., Finch, C.F. (2015), *From monocausality to systems thinking: a complementary and alternative conceptual approach for better understanding the development and prevention of sports injury*, in «Inj. Epidemiol.», 2 (1), p. 31. https://doi.org/10.1186/s40621-015-0064-1

Hume, D. (1739), *A Treatise of Human Nature*, in L.A. Selby, M.A. Bigge (eds.), Clarendon Press, Oxford.

Ilardo, M.L. (2023), *Vaccine Safety Pharmacovigilance: Individual causality assessment of AEFIs* [P.h.D. Thesis], Università Politecnica delle Marche, Ancona.

Iqbal, M. (2019), *Known Risks and Unknown Risk*, MI, URL = <https://mudassiriqbal.net/known-risk-and-unknown-risks/>.

IRGC (2018), *Guidelines for the governance of systemic risks*, EPFL, Lausanne.

ISO 31000 (2018), *Risk management Guidelines*, URL = <https://www.iso.org/standard/65694.html>.

Joffe, M., Gambhir, M., Chadeau-Hyam, M. *et al.* (2012), *Causal diagrams in systems epidemiology*, in «Emerg Themes Epidemiol», 9 (1). https://doi.org/10.1186/1742-7622-9-1

Kim, S.D. (2012), *Characterizing unknown unknowns*, paper presented at PMI® Global Congress 2012, Vancouver, British Columbia, Project Management Institute, Newtown Square (PA), URL = <https://www.pmi.org/learning/library/characterizing-unknown-unknowns-6077>.

Kóbor, A., Tóth-Fáber, E., Kardos, Z. *et al.* (2023), *Deterministic and probabilistic regularities underlying risky choices are acquired in a changing decision context*, in «Sci Rep», x 13, p. 1127. https://doi.org/10.1038/s41598-023-27642-z

Koeske, G.F. (1992), *Moderator variables in social work research*, in «Journal of Social Service Research», 16 (1-2), pp. 159-178. https://doi.org/10.1300/J079V16N01_08

Kramer, M.S. (1988), *Clinical epidemiology and biostatistics: a primer for clinical investigators and decision-makers*, Springer-Verlag, Berlin.

Kuliesas, A. (2017), *Venturing into Unknown: Unknown Project Risks and how to handle them*, Real Life Project Management Series, URL = <https://www.linkedin.com/pulse/venturing-unknown-project-risks-how-handle-them-arturas-kuliesas/>.

Lagiou, P., Adami, HO., Trichopoulos, D. (2005), *Causality in cancer epidemiology*, in «Eur J Epidemiol», 20, pp. 565-574. https://doi.org/10.1007/s10654-005-7968-y

Landes, J., Osimani, B., Poellinger, R. (2018), *Epistemology of causal inference in pharmacology: Towards a framework for the assessment of harms*, in «European Journal for Philosophy of Science», 8 (1), pp. 3-49. https://doi.org/10.1007/S13194-017-0169-1/FIGURES/4

Laniak, G.F., Olchin, G., Goodall, J., Voinov, A., Hill, M., Glynn, P., Hughes, A. *et al.* (2013), *Integrated environmental modeling: A vision and roadmap for the future*, in «Environmental Modelling & Software», 39, pp. 3-23. https://doi.org/10.1016/j.envsoft.2012.09.006

Lebiu, G. *et al.* (2017), *Il Nesso Di Causalità: Definizioni A Confronto*, Compartosanita.It, URL = <http://www.compartosanita.it/nesso-causalita-definizioni-confronto/>.

Lewis, D. (1973), *Counterfactuals*, Blackwell, Oxford.

Lewis, D. (1986), *Postscripts to 'causation'*, in Id., *Philosophical Papers: Volume II*, Oxford University Press, Oxford, pp. 172-213.

Lucas, K. (2020), *Theory of systemic risks: Insights from physics and chemistry*, in «Risk Analysis», 42 (9), pp. 1935-1944. https://doi.org/10.1111/risa.13558.

Lucas, K., Renn, O., Jaeger, C. (2018), *Systemic risks: Theory and mathematical modeling*, in «Advanced Theory and Simulations», 1 (11). https://doi.org/10.1002/adts.201800051.

Mackie, J.L. (1843), *The Cement of the Universe: A Study of Causation*, Clarendon Press, Oxford.

Mill, J.S. (1843), *A System of Logic, Ratiocinative and Inductive*, J.W. Parker, London.

Mota, D.M., Kuchenbecker, R. de S. (2017), *Causality in Pharmacoepidemiology and Pharmacovigilance: a theoretical excursion*, in «Revista Brasileira de Epidemiologia», 20 (3), pp. 475-486. https://doi.org/10.1590/1980-5497201700030010

Mumford, S., Anjum, R.L. (2011), *Getting Causes From Powers*, Oxford University Press, Oxford.

Neyman, J. (1960), *In Determinism in Science and New Demands on Statisticians*, in «Journal of the American Statistical Association», 55 (292), pp. 625-639. https://doi.org/10.1080/01621459.1960.10483363

OECD (2003), *Emerging risks in the 21st century: An agenda for action*, Paris, France, URL = <https://www.oecd.org/sti/futures/globalprospects/19134071.pdf >.

Osimani, B. (2010), *Pharmaceutical risk communication: Sources of uncertainty and legal tools of uncertainty management*, in «Health, Risk & Society», 12 (5), pp. 453-469. https://doi.org/10.1080/13698575.2010.509493

Osimani, B. (2013), *The precautionary principle in the pharmaceutical domain: A philosophical enquiry into probabilistic reasoning and risk aversion*, in «Health, Risk & Society», 15 (2), pp. 123-143. https://doi.org/10.1080/13698575.2013.771736

Osimani, B. (2014), *Philosophy of Pharmacology: Safety, Statistical Standards and Evidence amalgamation*, in *ERC Starting Grant: Research Proposal [Part B2]*, URL = <https://www.mcmp.philosophie.uni-muenchen.de/research/research_projects/phil_pharma/osimaniercproposal.pdf>.

Osimani, B. (2020), *Epistemic Gains and Epistemic Games: Reliability and Higher Order Evidence in Medicine and Pharmacology*, in A. LaCaze, B. Osimani (eds.), *Uncertainty in Pharmacology: Epistemology, Methods, and Decisions (Boston Studies in the Philosophy and History of Science)*, Springer, Cham, pp. 345-374.

Osimani, B., Ilardo, M.L. (2022), *«Nessuna correlazione»: gli strumenti per la valutazione del nesso causale tra vaccinazione ed evento avverso*, in E. Lello, N. Bertuzzi (eds.), *Dissenso informato. Pandemia: Il Dibattito Mancato E Le Alternative Possibili*, Lit Edizioni s.a.s., Castelvecchi, Roma, pp. 167-185.

Osimani, B., Mignini, F. (2015), *Causal assessment of pharmaceutical treatments: why standards of evidence should not be the same for benefits and harms?*, in «Drug Safety», 38 (1), pp. 1-11. https://doi.org/10.1007/S40264-014-0249-5

Papanikolaou, P.N., Christidi, G.D., Ioannidis, J.P.A. (2006), *Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies*, in «Can Med Assoc.», 174 (5), pp. 635-641. https://doi.org/10.1503/cmaj.050873

Parascandola, M. (1998), *What Is Wrong With The Probability Of Causation?*, in «Jurimetrics», 39 (1), pp. 29-44. http://www.jstor.org/stable/29762583

Parascandola, M. (2011), *Causes, risks, and probabilities: probabilistic concepts of causation in chronic disease epidemiology*, in «Preventive Medicine», 53 (4-5), pp. 232-234. https://doi.org/10.1016/j.ypmed.2011.09.007

Parascandola, M., Weed, D.L. (2001), *Causation in epidemiology*, in «Journal of Epidemiology and Community Health», 55 (12), pp. 905-912. https://doi.org/10.1136/JECH.55.12.905

Pearl, J. (2009), *Causality: Models, Reasoning, and Inference (2nd ed.)*, Cambridge University Press, Cambridge, URL = <https://doi.org/10.1017/CBO9780511803161>.

Pearl, J. (2000), *Causality: Models, reasoning, and inference* (Vols. 19, 2), Cambridge University Press, Cambridge.

Reiss, J. (2015), *Causation, Evidence, and Inference*, Routledge, New York.

Reiss, J. (2016), *Causality and Causal Inference in Medicine*, in M. Solomon, J.R. Simon, H. Kincaid (eds.), *Routledge Companion to Philosophy of Medicine*, Routledge, New York, pp. 58-70.

Renn, O., Laubichler, M., Lucas, K., Kröger, W., Schanze, J., Scholz, R.W., Schweizer, P.J. (2022), *Systemic Risks from Different Perspectives*, in «Risk Analysis», 42, pp. 1902-1920. https://doi.org/10.1111/risa.13657

Rocca, E., Anjum, R.L. (2020a), *Complexity, reductionism and the biomedical model*, in R.L. Anjum, S. Copeland, E. Rocca (eds.), *Rethinking causality, complexity and evidence for the unique patient: A CauseHealth resource for healthcare professionals and the clinical encounter*, Springer, Cham, pp. 75-94. https://doi.org/10.1007/978-3-030-41239-5_5

Rocca, E., Andersen, F. (2017), *How biological background assumptions influence scientific risk evaluation of stacked genetically modified plants: An analysis of research hypotheses and argumentations*, in «Life Sciences, Society and Policy», 13 (1), pp. 1-20. https://doi.org/10.1186/s40504-017-0057-7

Rocca, E., Anjum, R.L. (2020b), *Causal Evidence and Dispositions in Medicine and Public Health*, in «International Journal of Environmental Research and Public Health», 17 (6), p. 1813. https://doi.org/10.3390/IJERPH17061813

Rocca, E., Anjum, R.L., Mumford, S. (2020), *Causal Insights from Failure: Post-marketing Risk Assessment of Drugs as a Way to Uncover Causal Mechanisms*, in A. LaCaze, B. Osimani (eds.), *Uncertainty in Pharmacology: Epistemology, Methods, and Decisions*, Springer International Publishing, Cham, pp. 39-57. https://doi.org/10.1007/978-3-030-29179-2_2

Rosa, E.A. (1998), *Metatheoretical foundations for post-normal risk*, in «Journal of Risk Research», 1 (1), pp. 15-44, doi: 10.1080/136698798377303

Rossi, B. (2000), *Analisi del concetto di casualità nel diritto penale: le tesi*, In Redazione, URL = <https://www.diritto.it/concetto-casualita-dottrina-giurisprudenza/>.

Rothman, K.J. (1976), *Causes*, in «American Journal of Epidemiology», 104 (6), pp. 587-592. https://doi.org/10.1093/OXFORDJOURNALS.AJE.A112335

Rothman, K.J. (2012), *What Is Causation?*, in Id., *Epidemiology: An Introduction*, Oxford University Press, New York, pp. 23-37, URL = <https://global.oup.com/us/companion.websites/9780199754557/pdf/2e-Chap3.pdf>.

Rothman, K.J., Greenland, S. (2005), *Causation and causal inference in epidemiology*, in «American Journal of Public Health», 95 Suppl 1, S144-S150. https://doi.org/10.2105/AJPH.2004.059204

Russo, F., Williamson, J. (2007), *Causality and Probability in the Sciences*, College Publications, London.

Salmon, W.C. (1998), *Causality and Explanation*, in *Oxford Academic*, Oxford University Press, Oxford. https://doi.org/10.1093/0195108647.001.0001

Schanze, J., Trümper, J., Burmeister, C., Pavlik, D., Kruhlov, I. (2012), *A methodology for dealing with regional change in integrated water resources management*, in «Environmental Earth Sciences», 65 (5), pp. 1405-1414. https://doi.org/10.1007/s12665-011-1311-6

Scheffer, M. (2010), *Complex systems: Foreseeing tipping points*, in «Nature», 467, pp. 411-413. https://doi.org/10.1038/467411a

Schweizer, P.J. (2021), *Systemic risks – concepts and challenges for risk governance*, in «Journal of Risk Research», 24 (1), pp. 78-93. https://doi.org/10.1080/13669877.2019.1687574

SEP (2022), *Risk*, Stanford Encyclopedia of Philosophy, URL = <https://plato.stanford.edu/entries/risk/>.

Sexton, K. (2015), *Cumulative health risk assessment: Finding new ideas and escaping from the old ones*, in «Human and Ecological Risk Assessment», 21 (4), pp. 934-951. https://doi.org/10.1080/10807039.2014.946346

Shimabukuro, T.T., Nguyen, M., Martin, D., Destefano, F. (2015), *Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS) HHS Public Access*, in «Vaccine», 33 (36), pp. 4398-4405. https://doi.org/10.1016/j.vaccine.2015.07.035

Simon, M.A. (1992), *Causation, liability and toxic risk exposure*, in «Journal of Applied Philosophy», 9 (1), pp. 35-44. http://www.jstor.org/stable/24353539

Smith, D., Fischbacher, M. (2009), *The changing nature of risk and risk management: The challenge of borders, uncertainty and resilience*, in «Risk Management», 11, pp. 1-12. https://doi.org/10.1057/rm.2009.1

Sottosanti, L. (2015), *Il Risk Management System: le aspettative da parte delle Autorità*, AIFA, URL = <https://www.aifa.gov.it/sites/default/files/2015-11-30_Sottosanti-MS_30112015.pdf>.

Spohn, W. (1990), *Direct and indirect causes*, in «Topoi», 9 (2), pp. 125-145. https://doi.org/10.1007/BF00135893

SRA (2015), *Risk Analysis Foundations*, Society for Risk Analysis, URL = <https://li338-15.members.linode.com/news/discussion-paper-foundations-risk-analysis-developed-sra>; <https://www.sra.org/wp-content/uploads/FRASG/FoundationsMay7-2015-sent-x.pdf>.

Summerer, K. (2013), *Accertamento del nesso normativo: la formula della condicio sine qua non e il confronto tra evento reale ed evento ipotetico*, in M. Clarich, A. Gentili, F. Giunta, M. Jori, M. Taruffo (eds.), *Causalità ed evitabilità: Formula della condicio sine qua non e rilevanza dei decorsi causali ipotetici nel diritto penale*, Edizioni ETS, Pisa, pp. 389-394.

Suppes, P. (1970), *A Probabilistic Theory of Causality*, in «Acta Philosophica Fennica», fasc. XXIV.

Susser, M. (1973), *Causal thinking in the health sciences: concepts and strategies of epidemiology*, Oxford University Press, New York.

Taleb, N.N. (2007), *The Black Swan. The Impact of the Highly Improbable*, Penguin, London.

The Science and Environmental Health Network, *Wingspread Statement on the Precautionary Principle*, Wingspread Conference on the Precautionary Principle (1998, January 26), URL = <https://www.gdrc.org/u-gov/precaution-3.html>.

U.S. EPA (2003), *Framework for cumulative risk assessment,* (PA/630/P-02/001A May 2003), Washington, DC: Risk Assessment Forum U.S. Environmental Protection Agency, Office of Research and Development, URL = <https://www.epa.gov/sites/default/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf>.

UNDRR (2023), *Deterministic & Probabilistic Risk. PreventionWeb, Sendai Framework for disaster risk reduction 2015-2030. Sustainable development goals*, URL = <https://www.preventionweb.net/understanding-disaster-risk/key-concepts/deterministic-probablistic-risk>.

van Asselt, M. (2000), *Perspectives on uncertainty and risk*, Springer, Heidelberg.

Vandenbroucke, J.P. (2008), *Observational research, randomised trials, and two views of medical science*, in «PLoS Medicine», 5 (3), pp. 0339-0343. https://doi.org/10.1371/JOURNAL.PMED.0050067

Vose, D. (2008), *Risk Analysis: A Quantitative Guide*, Wiley & Sons, Chichester.

WHO (2019), *Causality assessment of an adverse event following immunization (AEFI): User manual for the revised WHO classification (2nd Ed.)*, URL = <https://apps.who.int/iris/bitstream/handle/10665/340802/9789241516990-eng.pdf?sequence=1&isAllowed=y>.

WHO-HIS-EMP (2013), *Causality assessment of an adverse event following immunization (AEFI): User manual for the revised WHO classification*, pp. 34-35, URL = <http://apps.who.int/iris/bitstream/handle/10665/80670/9789241505338_eng.pdf?sequence=1>

Williams, P.R.D., Dotson, G.S., Maier, A. (2012), *Cumulative risk assessment (CRA): Transforming the way we assess health risks*, in «Environmental Science and Technology», 46 (20), pp. 10868-10874. https://doi.org/10.1021/es3025353

Woodward, J. (2003), *Making Things Happen: A Theory of Causal Explanation*, Oxford University Press, New York.

Zappulla, C. (2019), *I Modelli Dello Sviluppo E Del Rischio,* URL = <https://www.unipa.it/persone/docenti/z/carla.zappulla/.content/documenti/I-modelli-dello-sviluppo-e-del-rischio.pdf>.

Abstract

Risk, often uncertain and contextual event, is intricately intertwined with causality, which shapes beliefs, risk perception and decisions. This study aims to: (i) highlight the intrinsic link between risk and causality, examining diverse causality notions underlying distinct risk concepts, and (ii) outline risk-emergent contexts and epistemological bases for operational strategies. We thus address epistemological implications of handling and assessing risk in different contexts such as those related with cause-and-effect, complex causality, probabilistic causality, and Bayesian causality accounts.

Keywords: risk; causation; risk perception; risk assessment and management; complexity; epistemological implications; operational strategies.

Maria Laura Ilardo, Marta Bertolaso
Research Unit of Philosophy of Science and Human Development,
Department of Science and Technology for Sustainable Development
and One Health, University Campus Bio-Medico di Roma
marialaura.ilardo@unicampus.it