

# An Epistemic Analysis of the Precautionary Principle

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## Un análisis epistémico del principio de precaución

**ABSTRACT:** The paper addresses charges of risk and loss aversion as well as of irrationality directed against the precautionary principle (PP), by providing an epistemic analysis of its specific role in the safety law system. In particular, I contend that: 1) risk aversion is not a form of irrational or biased behaviour; 2) both risk and loss aversion regard the form of the utility function, whereas PP rather regards the information on which to base the decision; 3) thus PP has formally nothing to do with risk or loss aversion but rather with risk awareness; 4) PP removes a fictional construct in the legal system, according to which any hazard should be ignored and denied until it is scientifically proven; 5) the quandary originates in the tension between current methods of evidence evaluation, and the logic underlying PP which demands for a probabilistic epistemology.

**RESUMEN:** Mediante un análisis epistémico de su rol en la legislación sobre seguridad, respondo a las críticas de irracionalidad realizadas al principio de precaución (PP), así como a las de aversión al riesgo y a la pérdida. Sostengo que 1) la aversión al riesgo no es una forma de conducta irracional o sesgada; 2) la aversión al riesgo y a la pérdida afectan a la forma de la función de utilidad, pero el PP se refiere a la información sobre la que basar la decisión; 3) más que con la aversión, el PP tiene que ver con la consciencia del riesgo; 4) el PP elimina un constructo ficticio en el sistema jurídico, según el cual cualquier amenaza debe ignorarse hasta que sea probada científicamente; 5) el problema surge en la tensión entre métodos de evaluación de la evidencia, así como de la lógica subyacente al PP, que demanda una epistemología probabilística.

**KEYWORDS:** precautionary principle, risk, safety, health, law

**PALABRAS-CLAVE:** principio de precaución, riesgo, seguridad, salud, Derecho

### 1. The precautionary principle: historical and conceptual background

In democratic societies restriction of persons' freedom by the state or any legal authority is justified only in highly limited contexts and for strictly specified purposes. Among these, the first (and for liberalist thinkers, the only legitimate) one is the prevention of unacceptable harm to entities worth of protection. Violation of the privacy right in any form requires also a strong evidence basis that the person's activity indeed leads to the expected harm. The causal link must be certain. The precautionary principle constitutes an amendment to this clause in that it relaxes the requirement of certain causal link in the face of relevant threat for the human or animal health or for the environment (see Jensen, 2002 for a theoretical and Di Fabio, 1994 as well as Kriebel et al., 2001 for a historical contextualization).

The first international documents which refer to the precautionary principle were emanated in relation to North Sea pollution. The First Conference for the Protection of the North Seas (Bremen, 1st November, 1984) asserts that States "must not wait for proof of harmful effects before taking actions"; the



second Conference (London, 24-25 November, 1987) makes explicit reference to the precautionary attitude and insists that “[...] a precautionary approach is necessary which requires to control input of such substances *even before a causal link has been established by absolutely clear scientific evidence*” (art. VII). The declaration of the Third Conference held in The Hague, which was released on 8 March 1990, states that the participants: “will continue to apply the precautionary principle, that is to take action to avoid potentially damaging impacts of substances that are persistent, toxic and liable to bioaccumulate *even where there is no scientific evidence to prove a causal link between emissions and effects*” (my emphasis). The Earth Summit in Rio de Janeiro, 1992, finally sanctions the precautionary principle and extends it to the global environment: “Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.” (UNCED, 1993, principle 15). The so-called Wingspread Statement formulated by Raffensperger and Tickner (1999) reads on the same vein: “When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically” (pp. 353-354).

Also the European Commission has emanated a document on the precautionary principle (2000), where its domain of application is extended from the environmental field to all cases “where scientific evidence is insufficient, inconclusive or uncertain and there are indications through preliminary objective scientific evaluation that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the chosen level of protection”.

Thus, the main distinctive point of the precautionary principle consists in relaxing the requirement of certain causal link between suspected polluter and dangerous effects as a condition for allowing coercive restriction of potentially harmful activities. This has important epistemological and methodological implications, which have not been sufficiently considered yet and which have led to much of the criticisms addressed against the precautionary principle. In fact, because, according to the precautionary principle, lack of scientific certainty about the potential harm should no longer constitute an obstacle for risk preventive actions, this has encouraged the common reading of the precautionary principle as a norm which reverses the burden of proof between intervening authority and potentially polluting agent (see

for instance Marini, 2008, Hathcock, 2000). Given that the authority is no longer obliged to demonstrate that some human activities cause serious harm to the environment in order to be allowed to adopt adequate preventive measure; then it seems that a logical consequence of this is that it is the potential polluter who has to prove that activities *do not* cause any serious harm to the environment in order to postpone these measures.

This reading may justify criticisms of the precautionary principle as a paralyzing norm which stifles innovation and which is dictated by a non-neutral attitude towards risk. Bodansky (1994) says: "although proponents have had a hard time agreeing on its precise meaning, broadly speaking the precautionary principle says that, with respect to the environment, we should err on the side of caution" (p. 203); [...] the precautionary principle is not neutral towards uncertainty – it is biased for safety" (209). On this basis, Apel (2002) even adduces that the precautionary principle violates the principle of utility maximization. Hansson interprets it as a maximin rule (1997) and Sunstein (2003, 2005) depicts the precautionary principle as loss aversive.

Another related cause of confusion which has also propped criticisms of risk aversion against the precautionary principle has arisen as a byproduct of a semantic analysis (Sandin, 2007, 2004; Sandin et al. 2002) based on the etymological association with the action of *averting* risks. This semantics, which ultimately originates in Hans Jonas' groundbreaking philosophical analysis "The imperative of responsibility" (1979) – and can be also traced back to Beck's (1986) sociological analysis – has ended up by screening off the purely cognitive dimension of the precautionary principle (as briefly explained above) which constitutes its real novelty (see also Fisher, 2002: 15 on this point). Also, this semantics gives support to the various charges addressed against the precautionary principle as a vague (Morris, 2000; McDonald, 2006; Bernie and Boyle, 2002; Cameron, 1999: 242) and irrational norm determined by fearful emotions and lack of scientific objectivity (Sunstein, 2005, Miller and Conko, 2000).

All these charges have ended up by strongly thwarting the impact of the precautionary principle both in the political arena and in the law (see for instance Marrani, 2008, for similar conclusions with respect to nanotechnology regulation at the European level).

However both these criticisms as well as the interpretation of the precautionary principle as a reverse onus rule do not take into account the following three essential points:

1. given that the precautionary principle drops the requirement of certain proof, the point is no longer to strive for proof (on one side or the other), but rather to decide what the already available evidence advises to do (there is a reversal of perspective, rather than of burden of proof);
2. actions are determined by taking into account evidence about the possible causal link as well as the magnitude of the risk. This is advocated for by the principle of proportionality (which is part of the precautionary principle, and is sometimes translated in terms of cost/effective measures as in the Rio declaration, or explicitly mentioned as such as in the European Commission document). The principle of proportionality roughly states that the higher the expected harm, the lower can be the probability of causal connection in order to allow for risk preventive measures;
3. the precautionary principle, by letting probabilistic hypothesis allow for coercive interventions, calls for an epistemology which is capable to deal with uncertainty and track it; this is at odds with much received methodological canon and here lies the hidden origin of the quandary.

I will analyze these issues by focusing on the implementation of the precautionary principle in the pharmaceutical domain, and in the final part I will concentrate my attention on the epistemological and methodological implications which follow from the precautionary principle with respect to the notion of uncertain evidence.

## 2. The precautionary principle in pharmaceutical regulation

The precautionary principle has been introduced in pharmaceutical regulation by the “Contergan” sentence (see Scheu, 2003, Di Fabio, 1994). The tranquilizer Contergan© (thalidomide), marketed in Germany between 1957 and 1961, caused severe birth defects to more than 8000 children—mainly produced by drug induced phocomelia—and fatally injured 2500 people. The Contergan sentence (18 December 1970) contributed to the development of a precautionary attitude in pharmaceutical regulation by introducing the *principle of well-founded suspicion*: “Before a risk suspicion can be founded scientifically, enough time may pass as to produce damage in some consumer. During this vacillation time, the risk has to be shouldered by the

pharmaceutical firm. Moreover, for the principle of inverse proportionality, inherited from danger prevention regulation, even very low probable suspicions ask for timely countermeasures". (Landesgericht (LG) Aachen, 18. 12. 1970 – 4 KMs 1/68, 15 – 115/67: Juristische Zeitung: 516)<sup>1</sup>. The principle of inverse proportionality says that the higher the value assigned to the endangered good, the lower can be the probability cut-off for approving interventions in its defense. Subsequently, the principle of well founded suspicion has been translated into a legally binding norm through art. 5 (prohibition of unsafe medicines: "Verbot bedenklicher Arzneimittel"). The German Medicines Act (Arzneimittelgesetz, AMG) is indeed the first law in western countries which translates the precautionary principle in hard law. It was enacted in 1976 and is the result of the political debate that followed the Contergan tragedy, and of the implementation of the European directives 75/318/EEC and 75/319/EEC that also followed this pharmaceutical catastrophe.

Article 5 of AMG establishes safety criteria for drug circulation and withdrawal. This norm stipulates prohibition of circulation for "unsafe drugs" and provides a definition thereof: unsafe drugs are those for which there is *well-founded suspicion* that, by adequate use, will have damaging effects exceeding a tolerable *threshold*, according to the knowledge of the medical science (§ 5 II) on the basis of available scientific data. Therefore this norm is articulated in three main components:

1. The degree of causal association between risk and danger source required for intervention need not be certain ("well-founded suspicion");
2. The level of causal association required for intervention is linked to the tolerance threshold, i.e. to the (un)balance between drug risk and benefit (principle of inverse proportionality: the greater the unbalance, the lower can be the probability of causal association);
3. The tolerance threshold is established through reference to the state of the art of relevant medical knowledge.

I will analyse these points in order and examine their interconnection in relation to the precautionary principle.

### 3. The principle of well founded suspicion

The historical importance of the principle of well founded suspicion is related to its fundamental role in moving pharmaceutical regulation from a “danger avoidance” system (Gefahrenabwehr), into a “risk prevention” system (Risikovorsorge). The difference between the danger avoidance and the risk prevention system lies in the kind of causal link between danger source and damage required for action. Whilst in the danger avoidance system a causal connection between danger source and damage needs to be established with certainty before the authority can intervene, in a risk prevention system it suffices to have a suspected causal connection between danger source and damage. In fact “well founded suspicion” is defined as “hypothesis of causal connection” (Scheu, 2003: 113).<sup>2</sup> This means that the authority and the industry are supposed to act as soon as the probability of a causal connection is sufficiently high with respect to the potential harm in relation to the potential benefit.

So, considering the benefits and harms associated with the technology under consideration and those associated with its alternative, one should intervene if the expected utility of the former is lower than the expected utility of the latter. This can be roughly formalized as an inequality between the net benefits of the two:

$$\sum P(b_i) \times U(b_i) - \sum P(h_i) \times U(h_i) < \sum P(b_j) \times U(b_j) - \sum P(h_j) \times U(h_j). \quad (1)$$

Where for any  $i$ ,  $b_i$  are the beneficial effects associated with the (health) technology and  $h_i$  the harmful effects known to be causally associated with it. Both are weighted by the probability of occurrence. Analogously, for any  $j$ ,  $h_j$  and  $b_j$  are harmful and beneficial effects associated with the alternative available option (in our case, the best drug already present in the market or, when there is no alternative treatment available, the disease which the drug under consideration is intended to cure).

Now, the difference between a risk prevention system (RPS), i.e. based on the precautionary principle, and a danger avoidance system (DAS), i.e. based on the requirement of certain causal connection, lies in the fact that in a DAS only harms are allowed to be included in the computation whose causal association with the danger source is certain: the others are simply neglected; instead in a RPS any harm is included which is suspected to be causally associated with the danger source, even if this association is not certain.

So by introducing the precautionary principle, the general rule transforms in the following. Intervene if:

$$\sum P(b_i) \times U(b_i) - \sum P(h_i) \times U(h_i) P(c_{hi}) < \sum P(b_j) \times U(b_j) - \sum P(h_j) \times U(h_j). \quad (2)$$

Where  $P(c_{hi})$  is the probability of causal association between health technology and the new detected harmful effects, even those for which the causal link has not been proven yet.  $P(c_{hi})$  must be 1 for any harm  $h_i$  to be included at all in the DAS computation so that (2) amounts to (1) in that case. Any harm, whose probability of causal association  $P(c_{hi})$  is less than one is not taken into account in (1).

Suppose you have a drug  $D_1$  whose expected utility, considering benefits and risks which are known to be causally associated with the drug, is 100 (so:  $\sum P(b_i) \times U(b_i) - \sum P(h_i) \times U(h_i) = 100$ ); furthermore, the disease which is cured by the drug can be associated with an expected utility of 70 (measured for instance by quality of life measures). Now a new side effect (SE) is detected, which, if really caused by the drug would reduce the drug expected utility to 60, i.e. less than the disease which is supposed to cure. However there is no certainty as to whether the drug really causes this side effect. Thus the decision matrix looks as follows.

	$D_1$ causes SE	$\neg(D_1$ causes SE)
Keep $D_1$ in the market (no withdrawal) $\neg w$	60	100
Withdraw $D_1$ : $w$	70	70

So one should withdraw the drug only if  $EU(w) > EU(\neg w)$  i.e. if the probability that the drug indeed causes the new detected harm is greater than .75, as the following elementary computation shows:

$$\begin{aligned} 70 &> x(60) + (1-x)(100) \\ 70 &> 60x + 100 - 100x \\ 70 &> -40x + 100 \\ 70 - 100 &> -40x \\ -30 &> -40x \\ 40x &> 30 \\ x &> \frac{3}{4} \end{aligned}$$

So if the probability of causal connection between drug and side-effect is more than .75, one should withdraw the drug from the market (see Osimani, Russo, Williamson, 2011 for a detailed treatment of this decision problem with reference to objective bayesianism).

Now let's see whether this reflects a risk averse strategy.



#### 4. Risk and loss aversion

Risk aversion is the phenomenon of preferring a sure(r) prize lottery to a risky/ier one even if the (expected) monetary value of the former is less than the expected monetary value of the latter. Risk aversion explains cases of apparent violation of the principle of expected utility maximization, where the agent is willing to pay a certain amount of money in order to get a sure prize instead of having to opt for a lottery with ambiguous outcome.

The phenomenon of risk aversion finds a mathematical explanation in the form of the utility function for monetary payoffs (Bernoulli, 1954). A concave utility function means for instance that the marginal utility attached to the same amount of good decreases marginally: Gaining 1000 dollars for a billionaire has a much lower utility than for a job-seeker. The consequence of this nonlinearity is that the prospect of receiving the average among two uncertain prizes for sure has a higher utility than the expected monetary value of a gamble between them.

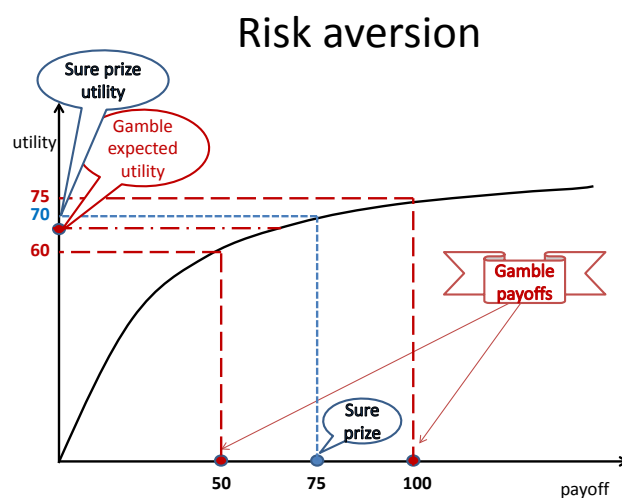


Fig. 1 Risk aversion curve. The x axis represents the monetary payoff, the y axis the associated utility. The expected utility of a 50/50 gamble between two prizes of 50 and 100 respectively, is exactly halfway between their utilities (red point in the y axis); instead the utility corresponding to the sure prize of 75 is 70 and itsituates higher than the expected utility of the gamble on the y axis.

Thus, risk aversion is perfectly rational provided that the utility function is concave, and the claim of irrationality addressed against the precautionary principle cannot be grounded on its supposed risk-aversive character.



Anyway, translated into our pharmaceutical problem, risk aversion should be modeled as the case in which the utility of a healthier and healthier condition decreases marginally. But the precautionary principle has nothing to do with this. Rather, it only concerns the recommendation to include in your health decision also those possible outcomes for which there is a probable but not certain causal association with the acts you are contemplating to opt for.

The precautionary principle has also been blamed of being loss-averse (Sunstein 2003, 2005). The phenomenon of "loss aversion" has been identified by Kahneman and Tversky (1984; see also Kahneman et al. 1991) as an explanation of the endowment effect (Knetsch, 1989). Loss aversion means that you perceive a higher dissatisfaction from losing something you already have, than you feel satisfied from gaining something of the same value (status quo bias). Loss aversion is the symmetric image of risk aversion for losses. It means that when faced with a sure loss or with a gamble whose expected disutility equals the sure loss, you prefer the gamble (thus you are risk prone for losses, while you are risk-averse for gains).

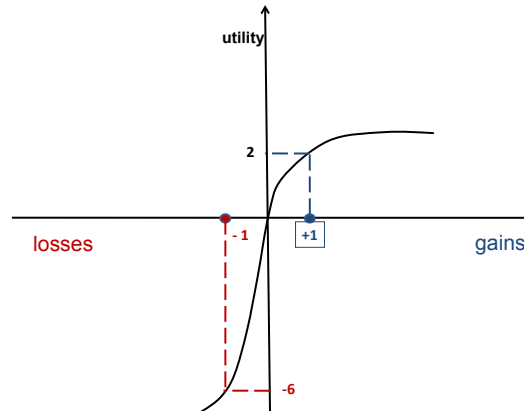


Fig. 2: Loss aversion. The utility function has different curves for gains and for losses respectively. This explains why losing an amount of payoff 1 provokes much more distress (- 6) than the satisfaction caused by gaining the same amount (+2) (adapted from Kahneman and Tversky 1984)

Recently, the existence of the phenomenon of loss aversion has been put into discussion because of a series of empirical studies which have failed to confirm it (Erev et al. 2008; Ert & Erev, 2008; Kermer, et al. 2006; Yechiam & Ert, 2007). But, again, much as important as these phenomena are for analyzing agents' behavior

in decisions under uncertainty, they just capture the role of the utility function in accounting for the agent's choice. However, as explained above, they do not concern the probability function and even less the causal beliefs associated with the relevant states. And because this is precisely where the precautionary principle comes into its own, risk (or loss) aversion and the precautionary principle do not belong one another.

The precautionary principle rather allows to integrate the uncertainty about the causal connection between drug and harm in the decision as follows. Whenever a new risk possibly associated with the drug is detected (development risk), a risk-benefit assessment needs to be made in order to determine whether this risk asks for intervention (for instance access restriction, approval suspension or product withdrawal). If the risk-benefit balance remains favorable for the product, then the detected risk can be considered irrelevant. Instead, if the newly detected risk changes the risk-benefit balance so as to make it unfavorable, then the precautionary principle simply recommends you to take it into consideration in your risk/benefit analysis even if the evidence regarding the causal link with the drug is inconclusive. The principle of proportionality then tells you that risk prevention/minimization measures should be proportional both to the importance of the unbalance and the evidence of causality: the probability of causal connection between a drug and a side-effect can be as low, for the drug to be retired, as the difference between the expected utility of retiring the drug from the market and that of letting it circulate [ $EU(\neg D) - EU(D)$ ] is big (see example above). Thus, the precautionary principle plays no role in constructing the form of the health utility function (this may be even convex or s-shaped), but with whether or not a gamble is at all introduced.

The precautionary principle does not violate expected utility either, on the contrary it prescribes to consider both the expected loss coming from letting the drug circulate in the market and from retiring it in consideration of a newly suspected side-effect.

Thus the issue is rather that before the introduction of the precautionary principle, risk was simply ignored: one should act as if one knew that the drug does not cause the side effect until contrary proven. But as stated above, this means that a lot of evidence concerning the possible causal link is not given any consideration unless it definitely confirms or refutes the hypothesis.

However, from the time a risk is completely unknown to the moment in which it is proven to be associated with a given technology there is period of evidence accumulation which constitutes a state of partial and imperfect (and asymptotically accumulating) knowledge. In this period we cannot pretend that we know nothing about this risk, and, on the other side we cannot pretend that the technology certainly causes harm. But this is precisely the kind of attitude which standard procedures of hypothesis testing ask us to assume.

Many misunderstandings around the precautionary principle have arisen precisely by the impossibility of combining it with norms of evidence evaluation which are deductive in principle (either the hypothesis is rejected or not with no grades in between). I will address this issue in the last part of the paper and I will briefly illustrate my point by drawing on the recent debate about the causal association between paracetamol (also known as acetaminophen) and asthma.

## 5. Evidence hierarchies and the epistemology of risk detection

In the last decades increased evidence of a possible association between paracetamol and increased risk of asthma has emerged through observational studies of various kinds (Seaton et al. 1994, Varner et al. 1998, Newson et al. 2000; Lesko et al. 2002, Barr et al. 2004; McKeever et al. 2005; Karimi et al. 2006; Beasley et al. 2008, 2011; Shaheen et al. 2008, Amberbir et al. 2011). Considering these studies, as well as his personal experience as a paediatrician pulmonologist, McBride (2011) claims that evidence of causal association between acetaminophen and asthma can by now be regarded as strong enough to warrant a change in prescription practice. McBride grounds his claim on the consistency of interdisciplinary evidence: 1) strength of the association displayed in comparative studies; 2) robustness of association across geography, culture and age; 3) dose-response relationship between acetaminophen exposure and asthma; 4) coincidence of time trends in acetaminophen use and asthma increase; 5) lack of other equally strong causal explanations; 6) relationship between asthma epidemic and per-capita sales of acetaminophen across countries; 7) plausible mechanism. However, some commentators have expressed adamant reluctance to accept such evidence as a sufficient basis for practice change and for establishing a causal relationship between acetaminophen and asthma, maintaining

that it does not result from randomized clinical trials (Eneli et al. 2005, Allmers et al. 2009, Johnson and Owby 2011, Karimi et al. 2006).

The difference between these two opposing perspectives lies in a different approach to scientific evidence. For McBride and other advocates of the restriction of paracetamol prescription (especially in paediatrics) observational evidence, even if it does not represent a litmus test for causality, provides sufficient evidence of causal connection as to warrant use restrictions. For sympathizers of classical hypothesis testing methods, this evidence provides no information until it is backed by controlled experiments. While the former view implicitly draws on a probabilistic epistemology which acknowledges uncertainty, the latter is grounded on a two-valued logic according to which hypotheses are either rejected or not with no grades in-between.

The reputation of Randomized Clinical Trials and Meta-analyses among practitioners is mainly due to the educational work carried out by proponents of Evidence-Based-Medicine, whose main concern has been to develop sound methods for distinguishing effective from non-effective therapies (see Howick, 2011 for a philosophical analysis). Whether or not their methodology, and the underlying epistemology, is adequate to the stated purpose has been object of a vivacious debate among philosophers (see Cartwright, 1989, 2007, Worrall 2007a,b, 2010, Papineau, 1994, Pearl, 2000, Teira 2011, Howson and Urbach 2006, Osimani forthcoming a, b) but my point here is to underlie the distinctive roles which such criteria have in evaluating causal inference of intended vs. unintended effects.

My point is that in the case of pharmaceutical harm, the deductive approach is problematic fundamentally for two reasons: 1) the first one has been already mentioned throughout the paper and precisely regards the fact that in this paradigm hypotheses cannot be expressed in probabilistic terms as it would be required for the implementation of the precautionary principle; 2) the second reason is that this sort of epistemology has been mainly developed for the purpose of hypothesis testing; whereas in the case of pharmaceutical harm the main issue is the detection of the effect itself.

The distinction between the task of testing intended effects vs discovering unintended ones has especially been emphasized in a series of papers mainly written by

epidemiologists in the last decade (Vandenbroucke and Psaty 2008, Vandenbroucke 2004, 2006, 2007, 2008, Psaty and Vandenbroucke 2008, Papanikolaou et al. 2006; Stricker and Psaty, 2004, Agency for Healthcare Research and Quality, 2007). These works support the view that evidence on pharmaceutical harms and benefits should be evaluated according to different criteria. Some have also proposed a reversal of the hierarchy for risk detection with respect to benefit assessment (Vandenbroucke 2008). In particular, Vandenbroucke (2008) endorses the idea that evidence hierarchies should be reversed upside down when the problem is not to test a benefit claim, but rather to discover an unintended effect of some health technology:

Hierarchy of Study Designs for Intended effects of Therapy	Hierarchy of Study Designs for Discovery and explanation
i. Randomised controlled trials	i. Anecdotal: case report and series, findings in data, literature
ii. Prospective follow-up studies	ii. Case-control studies
iii. Retrospective follow-up studies	iii. Retrospective follow-up studies
iv. Case-control studies	iv. Prospective follow-up studies
v. Anecdotal: case report and series	v. Randomised controlled trials

Table 1: Evidence hierarchy reversal for benefit vs. risk assessment (Vandenbroucke, 2008: 5).

Vandenbroucke presents several arguments in support of such a proposal. I will just mention two of them: one methodological and one epistemological. The methodological one relates to the issue of confounding by selection: selection bias is less likely to affect observational studies with respect to adverse reactions because unintended effects, qua unintended, are not known in advance, and thus also not known by the drug prescriber, who cannot take them into consideration and thereby bias treatment allocation: "As a mirror image for adverse effects research, the doctor *knows that he is prescribing a drug to a particular patient, but he might not know the risk that this patient has of developing a particular adverse effect. [...] This achieves the same aim of breaking the link between prescribing and prognosis*" (Vandenbroucke, 2004: 1728). Because of this, observational studies concerning adverse reactions will not suffer from confounding in the same way as observational studies for intended effects do (Vandenbroucke and Psaty 2008, Vandenbroucke 2004, 2006, 2007, 2008, Psaty and Vandenbroucke 2008).

An indirect test for this presumption is provided by empirical studies which find no systematic difference of risk estimation for common side effects in randomized v. observational studies (Papanikolaou et al., 2006, Benson and Hartz, 2000; Concato et al. 2000).

The second point advanced by Vandenbrouke in defence of his hierarchy reversal draws on epistemological considerations and regards the distinction between the context of discovery and the context of evaluation. As he properly points out, the context of discovery is characterized by serendipity, chancy detection of new phenomena and sudden explanation of puzzling phenomena through juxtaposition of papers in the literature. The context of evaluation instead is focused on confirming whether the insights gained through these various means really hold (Vandenbroucke, 2008: 1-7). Discovery is focused on explanation and hypothesis generation; evaluation instead, on hypothesis testing or confirmation, and research methods differ in the opportunities they offer with respect to either of these goals. Thus, far from constituting a second-best choice, case series (and single case reports) as well as findings in data and literature are a privileged tool for risk detection (Stricker and Psaty, 2004).

Vandenbrouke's line of defense of hierarchy reversal grounds on the idea that the assessment of efficacy can be assimilated to hypothesis testing, whereas the discovery of unintended effects cannot be dealt with adequately by this sort of dichotomic methods.

For the purpose of the present discussion another point should be added, and precisely the fact that the precautionary principle demands to express the degree of confidence in the hypotheses under consideration in probabilistic terms. This is not possible within classical hypothesis testing techniques.

Statistical hypothesis-testing is a kind of approach which expressly follows a Popperian hypothetico-deductive method of scientific enquiry. Unfortunately, the sort of statistics grounded on this epistemology is inherently non-committal towards the tested hypothesis: the results it delivers are expressed as a probability statement *on the evidence*, provided that the null hypothesis is *true* (where the null hypothesis is the negation of the hypothesis of interest). Thus they leave no room for probabilistic assignments to the hypothesis of interest (e.g. how probable it is that the drug indeed causes an observed side effect).

This sort of *aut-aut* epistemology cannot adequately accommodate situations of the sort dealt with by the precautionary principle. In the case of hazard discovery, this has important practical and ethical implications in that putting unreasonable constraints on the kind of evidence which is allowed to count as valid for justifying our benefit-risk assessment concerning the drug, may severely limit our capacity of action and thus of risk prevention.

The charges addressed against the precautionary principle originate from the tension between a legal instrument which acknowledges uncertainty and a system of evidence evaluation which instead still rests on a two-valued deductive epistemology.

## 6. Conclusion

The analysis of the precautionary principle presented here is epistemic in two senses. In one sense it explains what the precautionary principle is and what it is not. It is a norm which amends the general requirement that a causal link must be certain before the state or any authority can enforce coercive restrictions upon the activity of an agent. It is not a risk or loss aversive norm in that it does not impact on the utility function related to the decisions under consideration. The second sense regards the epistemological and methodological implications introduced by the precautionary principle. These can be summarized in the demand for a probabilistic epistemology of hypothesis assessment. Charges against the precautionary principle can be better understood if we consider the tension between a legal instrument which acknowledges uncertainty and a system of evidence evaluation which is fundamentally grounded on a deductive epistemology whose scope – hypothesis rejection – is too limited for the purpose of risk management and prevention.

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## Notes

1. The sentence has also increased the responsibility sphere of the industry by introducing strict liability for pharmaceutical products. Until then, damage compensation was regulated by tort liability only, which required the assessment of negligence for liability attribution. This extension has been translated into norm through article 84 of the German Medicines Act.
2. This issue has been conceptualized differently in the German as well as European vs. U.S. regulation. Whereas in Germany the introduction of the principle of "well founded suspicion" has meant the relaxing of the causal assessment from certain to probable, pharmaceutical regulation in the U.S. (and FDA guidelines to the industry) are rather concentrated on the maintenance of a favorable risk/benefit balance. Even if the interpretation of safety signal (i.e. whether adverse events are caused by drugs or not) is part of the decision process which possibly leads to drug status change (included withdrawal), the uncertainty surrounding the safety signal is not treated separately from the risk-benefit assessment, but instead is part of the evaluation of the different options available.  
Section 505-1 [21USC §355-1] Point b of the Food and Drug Amendment Act (which concerns REMS, Risk Evaluation and Mitigation Strategies) defines Adverse Drug Experience as any adverse event associated with the use of a drug in humans whether or not considered drug related: the different options available when safety signals arise (use restriction, introduction of special contraindications and precautionary information, access restriction, ...) are elected in consideration of possible benefits and drawbacks implied by each with no explicitly separated consideration of the degree of causal assessment between suspected drug and detected signal. Hence, the precautionary principle as it is formalized in the German Medicines Act has no equivalent in U.S. even if on a practical level it is included in the risk management praxis.