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The Precautionary Principle and Pharmaceutical Risk Management

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Abstract

Although it is often vigorously contested and has several different formulations, the precautionary principle has in recent decades guided environmental policy making in the face of scientific uncertainty. Originating from a criticism of traditional risk assessment, the key element of the precautionary principle is the justification for acting in the face of uncertain knowledge about risks. In the light of its growing invocation in various areas that are related to public health and recently in relation to drug safety issues, this article presents an introductory review of the main elements of the precautionary principle and some arguments conveyed by its advocates and opponents. A comparison of the characteristics of pharmaceutical risk management and environmental policy making (i.e. the setting within which the precautionary principle evolved), indicates that several important differences exist. If believed to be of relevance, in order to avoid arbitrary and unpredictable decision making, both the interpretation and possible application of the precautionary principle need to be adapted to the conditions of pharmaceutical risk management.

Since adverse drug reactions continue to constitute a serious threat to public health, there is currently a widespread understanding of the need to renew systems and processes for the safety surveillance of drugs.[1,2] On an international level, an important manifestation of these efforts is the progress of the International Conference on Harmonisation (ICH) E2E guideline, which is intended to aid industry and regulators in the planning of pharmacovigilance activities.[3] Although the need to obtain better evidence and develop more efficient ways of promoting safe drug utilisation are most often emphasised, the possibility of improving related decision making has been acknowledged.[2] Often informal, decisions are occasionally dependent on the particular experts involved and the assumptions and logic underlying the decision may not be made explicit or adequately tested during the process. Quantitative methods for benefit/risk analysis have been proposed as a means of enhancing decision making related to pharmaceutical risk management.[4] Moreover, it has also been suggested that application of the precautionary principle could be relevant in this context.[2,5] Although some of its main ideas, e.g. the need for proactive monitoring of safety, can be traced in draft guidelines on pharmaceutical risk management, the precautionary principle is rarely explicitly debated by those involved in this area. Although it is often vigorously contested and has several different formulations, the precautionary principle has in recent decades guided environmental policy making in the face of scientific uncertainty. Moreover, its role has been further underscored by its appearance in international treaties and in national and international legislation.

In the light of its growing invocation in various areas related to public health and, recently, drug safety issues, the aim of this article is to present an

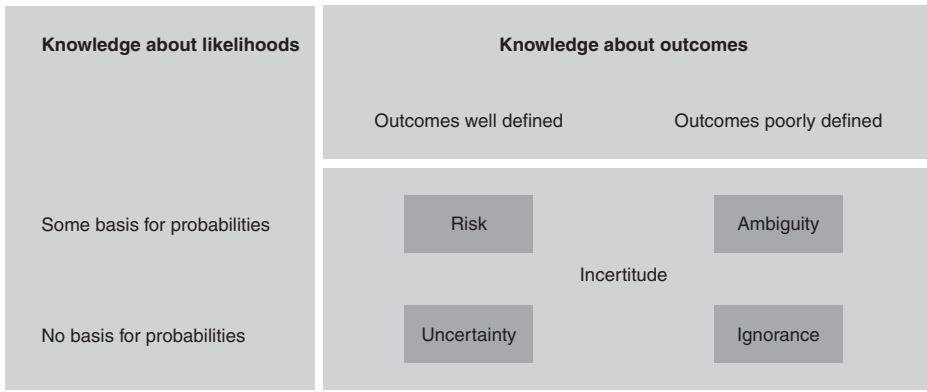

Fig. 1. The concepts of 'risk', 'uncertainty', 'ambiguity' and 'ignorance', reproduced from Stirling and Gee,[6] with permission from Public Health Reports.

introductory review of the main elements of the precautionary principle and some arguments that are conveyed by its advocates and opponents. Also, a comparison will be made of the characteristics of pharmaceutical risk management with those of environmental policy making, i.e. the field where most of the experience with the precautionary principle is derived from.

1. Risk and Uncertainty

The precautionary principle is intended as a guide to decision making in situations that are characterised by risk and uncertainty. Still, these concepts can be elusive and, therefore, it can be of relevance to briefly review some formal definitions that have been proposed in order to reduce confusion.[6] Figure 1 defines the relevant terms by categorising them in relation to the extent of knowledge about the outcomes and the likelihoods that they imply. Thus, the formal definition of *risk* is a condition under which it is possible both to define a comprehensive set of all possible outcomes and to assign probabilities to these. This is illustrated in the top left hand corner of figure 1. *Uncertainty* appears in the lower left hand corner of figure 1. It applies to a condition under which there is confidence in the completeness of the defined set of outcomes, but no valid basis for assigning probabilities to these outcomes. When there is some understanding of the likelihood that an event will occur, but sparse information on the nature of that outcome, *ambiguity* is thought to prevail. Lastly, in the lower right hand corner is the term *ignorance*, which is formally defined as a condition where information on possible outcomes and their probabilities are missing. Thus, this is the situation where the possibility exists of outcomes beyond previous considerations. In order to refer to all four conditions, without making the distinctions outlined, the term *incertitude* can be used. Whereas traditional risk assessment is best applied to situations characterised by risk, its proponents assert that the precautionary principle is needed to address uncertainty, ambiguity and ignorance.[6] The distinctions introduced here are not always applied rigorously in the literature, nor is it the case in this text. Also, some dispute exists as to whether risk assessment and risk management should be seen as two entirely separate entities, where the precautionary principle is applicable only to the latter. In this article, this constraint is not imposed.

2. The Evolution of the Precautionary Principle

Traditional risk assessment has usually involved the quantification of risk by means of scientific methods and a subsequent attempt to find an acceptable level of risk. The emergence of the precautionary principle can be traced from a critical analysis of this traditional approach that has been perceived as being too narrow, simplistic and not taking ignorance and uncertainty into account.[7,8] An additional argument underpinning the precautionary principle has been the perceived conservatism of traditional

science, which is seen as biasing conclusions toward the null hypothesis and thus indicating the absence of harmful effects.[9] For example, the standard application of a limit of '$p < 0.05$' for statistical significance will often reject many findings of causal associations because of a lack of statistical power or because of some imprecision or limited sensitivity of the estimated parameters. In the absence of traditional 'solid' evidence demonstrating damage or harm, necessary interventions have sometimes been deferred with serious consequences. Notable examples are the failures to act on warnings that were related to bovine spongiform encephalopathy or the use of asbestos. Hence, at the core of the precautionary principle is a justification for acting despite an uncertain knowledge about risks.

Although some predecessors can be discerned in various historic eras, the modern precautionary principle first appeared in German environmental policy in the 1970s, and the term 'precautionary principle' was introduced into English as a translation of the German word *Vorsorgeprinzip*.[7] An alternative translation of this word is the 'foresight principle', a phrase that elicits the importance of anticipatory action.[10] An early definition, framed in a rather unrelenting wording, appeared in the World Charter for Nature in 1982: "where potential adverse effects are not fully understood, the activities should not proceed".[11] This phrasing would reasonably rule out many activities at an early stage. However, later versions of the precautionary principle have tended to be more moderate and some new elements have been added to it. In recent years, two definitions have often been cited; the first one stems from the 1992 Rio Declaration on Environment and Development. In Principle 15 the Declaration states that "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".[12] The second definition, the Wingspread Statement, which was developed by advocates of the precautionary principle in 1998, uses a comparable definition and states that "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".[13] Moreover, this Statement emphasises four core elements of the principle:

1. Taking preventive action in the face of uncertainty.
2. Shifting the burden of proof to the proponents of an activity.
3. Exploring a wide range of alternatives to the possibly harmful actions.
4. Increasing public participation in decision making.

Further elaboration on the elements of the Wingspread Statement was completed in 2001 by The Lowell Statement on Science and the Precautionary Principle.[14] Lastly, in some versions, the precautionary principle has involved objectives as "promoting the cause of intrinsic natural rights" and "paying for past ecological debt".[15]

Although the elements of the Rio Declaration or the Wingspread Statement are not legally binding, the case is different within the EU where the precautionary principle has influenced legislation on several occasions.[16] The Maastricht Treaty of 1992 explicitly states that the EU's environmental policy shall be based on the precautionary principle. Later, in the Amsterdam Treaty of 1997, there was an implicit recognition of the relevance of the precautionary principle in relation to public health, an area of application that has since steadily grown in importance. At this point, it is important to note that neither the Maastricht Treaty nor the Amsterdam Treaty clearly define the precautionary principle in terms of its applicability or contents. Since the lack of definition could lead to unjustified use, the European Commission in 2000 issued a guideline in order to promote greater consistency in its application.[17] The communication states that "where action is deemed necessary, measures based on the precautionary principle should be, *inter alia*:

- *proportional* to the chosen level of protection,
- *non-discriminatory* in their application,
- *consistent* with similar measures already taken,
- *based on an examination of the potential benefits and costs* of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis),
- *subject to review,* in the light of new scientific data, and

• *capable of assigning responsibility for producing the scientific evidence* necessary for a more comprehensive risk assessment".

According to its proponents, because of its shift in perspective, the application of the precautionary principle entails a number of consequences.[7,10] Instead of a focus on the quantification of risks and limits of acceptability, decision makers are called upon to question whether an activity is needed and to what extent alternatives exist in order to achieve societal goals. Moreover, rather than presume that specific substances or economic activities are safe until proven dangerous, the precautionary principle establishes a presumption in favour of protecting the environment and public health in the face of uncertain risks. The call for increased participation and transparency in public health decision making has been justified by the allegedly broader perspective of an issue by the lay public, in contrast to narrow disciplinary viewpoints. If successful, this involvement could increase the quality, legitimacy and accountability of complex decisions. Finally, somewhat surprising is the recent appearance of the precautionary principle in intelligence analysis and as a rationale for nations to take pre-emptive action against perceived foreign threats.[18]

3. Objections to the Precautionary Principle

Over the years, the precautionary principle has been both invoked and criticised in contentious debates ranging from that on genetically modified food to global warming and mobile telephones. The criticism of the precautionary principle has been related to either its contents and implications or to the way in which it has been applied. The main objection emanates from concerns that, if applied rigidly, the precautionary principle could stifle discovery and scientific progress.[19] This could be a consequence of the encouragement of decision makers to take into account both uncertainty and ignorance. Seen this way and aiming to avoid all actions that may conceivably cause harm, hardly any action would ever be justified and the precautionary principle would become the principle of inaction, hostile to all innovation.[20] Furthermore, an unintended outcome of a relentless interpretation could be a failure to replace old and harmful technologies or the causing of new threats to the public's health. The latter has been the theme in the debate on the use of dichlorodiphenyltrichloroethane (DDT) for malaria control.[21] Also, a too precautionary standard for managing risks could create an abundance of 'false positives' that would ultimately lead to a waste of resources and distraction from real problems.[22]

A further criticism of the precautionary principle relates to its perceived vagueness, which is further complicated by the existence of multiple definitions and variability in interpretation.[23,24] For example, the level of the threat that is necessary to apply the precautionary principle ranges from 'serious and irreversible risks' in the Rio Declaration to presumably any risk in the Wingspread Statement. Moreover, the consideration of costs involved differs across the formulations and there is no guidance as to when the proponent of a technology has satisfactorily demonstrated its safety. The elusiveness of the precautionary principle poses less of a problem when it is applied as a general policy ambition. However, when transformed into a binding legal rule, the inherent ambiguity of the precautionary principle could result in arbitrary application by regulatory agencies and it could limit the capability of reviewing courts to perform their function in overseeing agency actions.[24] Thus, in this situation there would be a risk of misuse of the precautionary principle for other purposes, for example as a veil for trade protectionism. It has sometimes been claimed that the European ban on the import of North American beef (because of the use of growth hormones) and the delay in approving genetically engineered crops for sale in European markets, originated from concerns unrelated to the public health.[23]

Other objections to the proliferation of the precautionary principle focus on the precautionary principle's supposed lack of attention to the benefits of an activity and the risk of biased public participation when special interest groups are given too much sway.[20,25] Also, one may feel that the precautionary principle is superfluous and that most of its elements are obvious and only imply the kind of common sense thinking that has always been mankind's attribute. Hence, seen this way, the current debate on the precautionary principle is a reflection of a modern culture that, despite an unprecedented level of safety

Table I. A comparison between pharmaceutical risk management and environmental policy making

Factors related to the precautionary principle	Pharmaceutical risk management	Environmental policy making
Benefit/risks accrue to the same subject	+	–
Potential for individualisation of exposure	+	–
Potential for monitoring of exposed subjects	+	(–)
Frequency of unintended effects	+	(–)
Consent of the exposed	+	–
Premarketing data required on use in human subjects	+	(–)
Assessment of effects on the ecosystem/other species	(–)	+

+ indicates common; **(–)** indicates occasionally; **–** indicates rarely.

in many areas, is obsessed by risk aversion. A response to some of the objections to the precautionary principle has recently been formulated by one of its proponents.[22]

Finally, the conflict between traditional risk assessment and the precautionary paradigm can to some extent be seen as artificial, since the two approaches are not mutually exclusive.[8] Far from being in conflict, these two concepts can be consistent and even mutually reinforcing.[6]

4. The Precautionary Principle and Pharmaceutical Risk Management

With the recent appearance of the precautionary principle in relation to drug safety and pharmaceutical risk management, the debate on its relevance in this context appears to be in its early and tentative stage.[5,26] Still, some evident references to precautionary ideas could be noticed in a criticism of the failure to duly investigate the association between cardiovascular disease and the recently withdrawn cyclo-oxygenase (COX)-2 inhibitor rofecoxib.[27] Nonetheless, the greater part of the experience with the precautionary principle emanates from its application to environmental policy making. Clearly, with regard to a number of important aspects, several parallels exist between environmental policy making and pharmaceutical risk management. With only sparse and sometimes conflicting data, regulators in both areas have to make decisions that have potentially serious implications for the public health. The stress of the situation is sometimes aggravated by intense coverage by the media and pressure from those with financial interests in the outcome of the decision making. Moreover, both areas have dire experiences from previous failures where various stakeholders, with the benefit of hindsight, have blamed regulators for incompetence and negligence. Hence, it is easy to understand the desire for a 'guiding principle' that can help prevent future failures in regulatory decision making. Still, despite the similarities, a number of important differences exist. Table I represents an attempt to compare the characteristics of environmental policy making with that of pharmaceutical risk management; however, the classification of the variables is approximate and several exceptions exist.

Assessing the benefit/risk balance can be rather complicated in environmental policy making. In particular, this is true when benefits and risks accrue to different individuals, populations, generations or species. The use of DDT will provide a cheap and efficient means for controlling malaria in poor countries;[21] however, harmful effects could later afflict other parts of the ecosystem. Similarly, small island nations, with a low consumption of fossil fuels, will be the first to experience the consequences if the risk of a greenhouse effect and global warming turns out to be correct. Assessing the balance of effects of therapeutic drugs is usually more straightforward, as the individual patient gets both the benefits and the risks. One exception is the use of vaccines where limiting the spread of an epidemic benefits the whole population. The opportunities for focusing an exposure in the right direction are good in drug treatment. Based on a medical history and laboratory tests, vulnerable subgroups can be identified and excluded from exposure, leading to a favourable benefit/risk balance in those ultimately treated. Environmental pollutants are harder to control and can spread widely in a population or in an ecosystem. Likewise, the outcomes of an exposure to a therapeutic drug can fairly easily be monitored on an individual level and necessary adjustments of the therapy can be initiated in a timely manner. When

monitoring for potentially harmful effects from environmental exposures, observational study designs have limits in terms of finding unexposed control groups and identifying small but important hazards.[8] Essentially no therapeutic drugs are free from adverse drug reactions, but in the perspective of their intended benefits, there is a wide acceptance of risks involved and patients are only exposed if they have consented to receive the drug. This is a crucial point since environmental hazards, although involving a lower incidence of harmful effects, are spread without the consent of those exposed. Obviously, with respect to both therapeutic drugs and environmental pollutants, one should bear in mind that the true incidence and severity of harm may not be uncovered until a long period of time has elapsed. Although a clinical development programme, usually involving several randomised clinical trials, yields an abundance of information on the effects of a drug in humans (both healthy volunteers and vulnerable subgroups), the same investigations on potential environmental pollutants will never be feasible for ethical reasons. Lastly, concerns related to the effect on the whole ecosystem and species other than humans are common in environmental policy making. Although the same aspect can be of relevance when assessing pharmaceuticals in some instances,[28] this is rarely the case. Thus, in the light of its evolvement in a different setting, an appeal to the precautionary principle – as currently stated – may not always be appropriate in issues related to drug safety.

The current system for drug safety surveillance already addresses the precautionary principle's call for monitoring and the anticipation of outcomes beyond previous considerations. In the wake of the thalidomide disaster in the early 1960s, it was widely recognised that premarketing risk assessment had important limits. In an effort to improve the postmarketing safety surveillance of drugs, systems for spontaneous reporting of adverse drug reactions were successively implemented worldwide. At present, it is still the most important resource for identifying safety signals and complemented with various data-mining strategies,[29] unexpected adverse drug reactions can be detected. The value of spontaneous reports is clear in terms of finding rare adverse drug reactions that occur shortly after exposure. However, their utility is less obvious when assessing chronic effects or reactions that are manifested in the form of an increase of a common disease, e.g. diabetes mellitus.[30] In that respect, data-mining of healthcare databases and prescription registries may offer a useful approach to improve the safety surveillance of drugs.[31] Given the large number of false positive signals generated by various data-mining strategies,[29] a parsimonious application of the precautionary principle would be warranted in this area or else the number of market withdrawals would be unreasonable. In other respects, the precautionary principle may offer some fresh perspectives on current research paradigms. For example, one could question the routine application of the same limit for statistical significance (e.g. $p < 0.05$), no matter whether marginal benefits or serious adverse drug reactions are studied. Put in other words, when investigating risks of serious harm it may be more appropriate to be concerned with type II errors rather than type I errors.

5. Conclusion

Although at times vigorously contested, the precautionary principle has over the last decades evolved and influenced environmental policy making worldwide. Originating from a criticism of traditional risk assessment, the key element of the precautionary principle is the justification for acting in the face of uncertain knowledge about risks. More recent is its appearance in public health and in relation to drug safety issues. Rather than either embracing or rejecting the precautionary principle, studying the experience gained from its previous applications should be the way forward. If believed to be of relevance, in order to avoid arbitrary and unpredictable decision making, its interpretation and possible application need to be adapted to the conditions of pharmaceutical risk management.

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