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Frameworks for Quantitative Risk Assessment, Uncertainty, and Precaution

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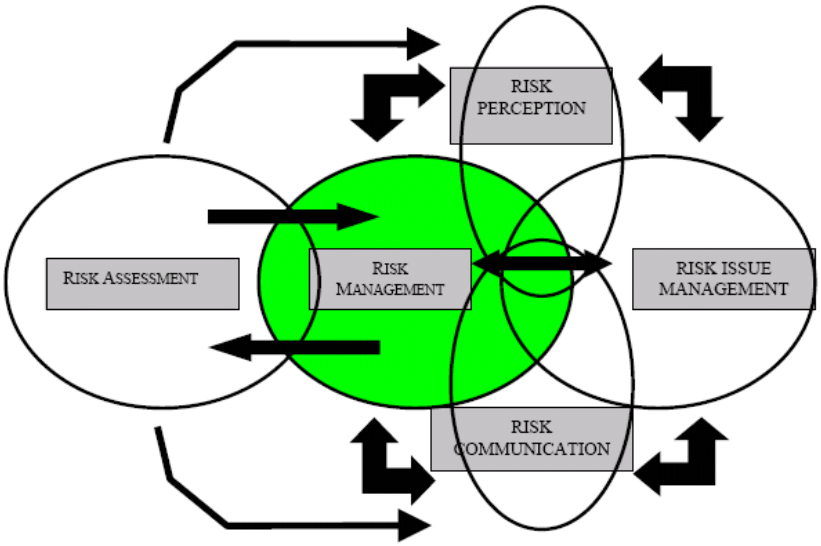
1 The Risk Labyrinth

Risk analysis is a portmanteau term for the several risk-related disciplines grouped within the "risk labyrinth" (see Figure 1). This labyrinth has many overlapping components with strong feedback loops among them. The component that this chapter focuses on is risk assessment (RA). Although the chapter focus is on RA, in policy terms risk management (RM) has central importance. Furthermore, in most cases of regulatory significance there is significant overlap and feedback between the two functions. For example, monitoring results obtained as a result of risk management decisions concerning a GM crop (see Chapter 3) can feed back to produce a revised risk assessment. Risk management goals should guide the nature and extent of a risk assessment. Consequently, attempts by regulators to artificially compartmentalise the two functions are likely to result in poorer risk regulation decisions except where the uncertainty in the RA is small. Because this book (and this chapter in particular) is concerned with the problem of significant uncertainty some reference to this interface is inevitable.

Figure 1: The Risk Labyrinth



1.1 Risk Assessment (RA)

RA is the practice of using observations about what we know to make predictions about what we don't know in order to draw conclusions about the likelihood of a risk or to make decisions about how best to control a particular risk. RA is a procedure informed by both science and judgment that, at heart, consists of identifying hazard–harm pairs and then determining the relationship between exposure to the hazard and the likelihood of resultant harm (the dose-response relationship). A typical example would be identifying exposure to the sun as a risk factor (the hazard) for skin cancer (the harm) and then elucidating quantitatively the form of the relationship, perhaps through epidemiological studies (Rogers 2003).

RA is a procedure for including science in decisions about whether and to what extent risks to health, safety, or the environment should be limited. However, in nearly all cases the science, and hence the RA, is beset by uncertainties (as distinct from variability, see for example Hattis, 2004). In general, we have only limited information about a population's varied exposures to chemicals (see Chapter 11), for example, or about the toxicological mode of action of a particular chemical once exposure occurs and how that might differ in different individuals, or about the interactions among multiple environmental and physiological characteristics.

Risk-related uncertainties are of three types, namely,

- Uncertainty about the effect (because the realisation of the harm is stochastic in nature);
- Uncertainty about the cause (because a realised harm may be due to any one of several hazards or a combination of hazards); and,
- Uncertainty about the given hazard-harm relationship (because of poor confidence in the hypothesised dose-response model or relationship).

The third type of uncertainty arises when there is insufficient knowledge about a postulated hazard-harm pair and is thus epistemic in nature. Epistemic uncertainty has particular relevance to precaution and the precautionary principle (see section 2 of this chapter).

For the risk assessor, details about exposures, effects, and interactions are generalized using assumptions and estimates of likelihood or estimates of the level of hazard that are likely to result in harm. Those assumptions are generally precautionary and the estimates can be modified using uncertainty factors to identify conditions under which a level of risk

realization is unlikely. Risk assessment is valuable because it provides a structured way to evaluate and draw conclusions from available scientific data, but it is at the same time limited by the nature and extent of the data. As the US National Academy of Sciences' report "*Science and Judgment in Risk Assessment*" (US NAS/NRC 1994) puts it:

> *The overall accuracy of a risk assessment hinges on the validity of the various methods and models chosen, which in turn are governed by the scope and quality of data. The degree of confidence that one can place in a risk assessment depends on the reliability of the models chosen and their input parameters (i.e., variables) and on how well the boundaries of uncertainty have been quantified for the input parameters, for the models as a whole, and for the entire risk-assessment process.*

The European Commission has instituted a programme to harmonise procedures for risk assessments in the human health and environmental protection fields. The First Report from this programme of work (EC 2000) acknowledges that the "hazard-harm" relationship consists of four steps, namely, *hazard identification, hazard characterisation, exposure assessment,* and *risk characterisation,* and that this process is based on "*Risk Assessment in the Federal Government: Managing the Process*", also called "the red book", by the US National Academy of Science's National Research Council (US NAS/NRC 1983). In fact, most RA systems in use are based on this NRC report (although the NAS/NRC version refers to "dose-response assessment" instead of hazard characterisation). However, there is continuing confusion about the hazard identification step, which involves identifying potential adverse effects of concern. The identification of a hazard *per se* does not translate into a risk unless exposure to the hazard results in a degree of harm. This is why the simpler "hazard-harm" formulation is to be preferred.

More Recently the European Food Safety Authority (EFSA) has issued a report on the RA of GMOs (EFSA 2005), which defines RA as:

> *"a process of evaluation including the identification of the attendant uncertainties, of the likelihood and severity of an adverse effect(s)/event(s) occurring to man or the environment following exposure under defined conditions to a risk source(s)" (EC, 2000). A risk assessment comprises hazard identification, hazard characterisation, exposure assessment and risk characterisation.*

> *The sequential steps in risk assessment of GMOs identify characteristics which may cause adverse effects, evaluate their potential consequence, assess the likelihood of occurrence and estimate the risk posed by each identified characteristic of the GMOs.* (emphasis added)

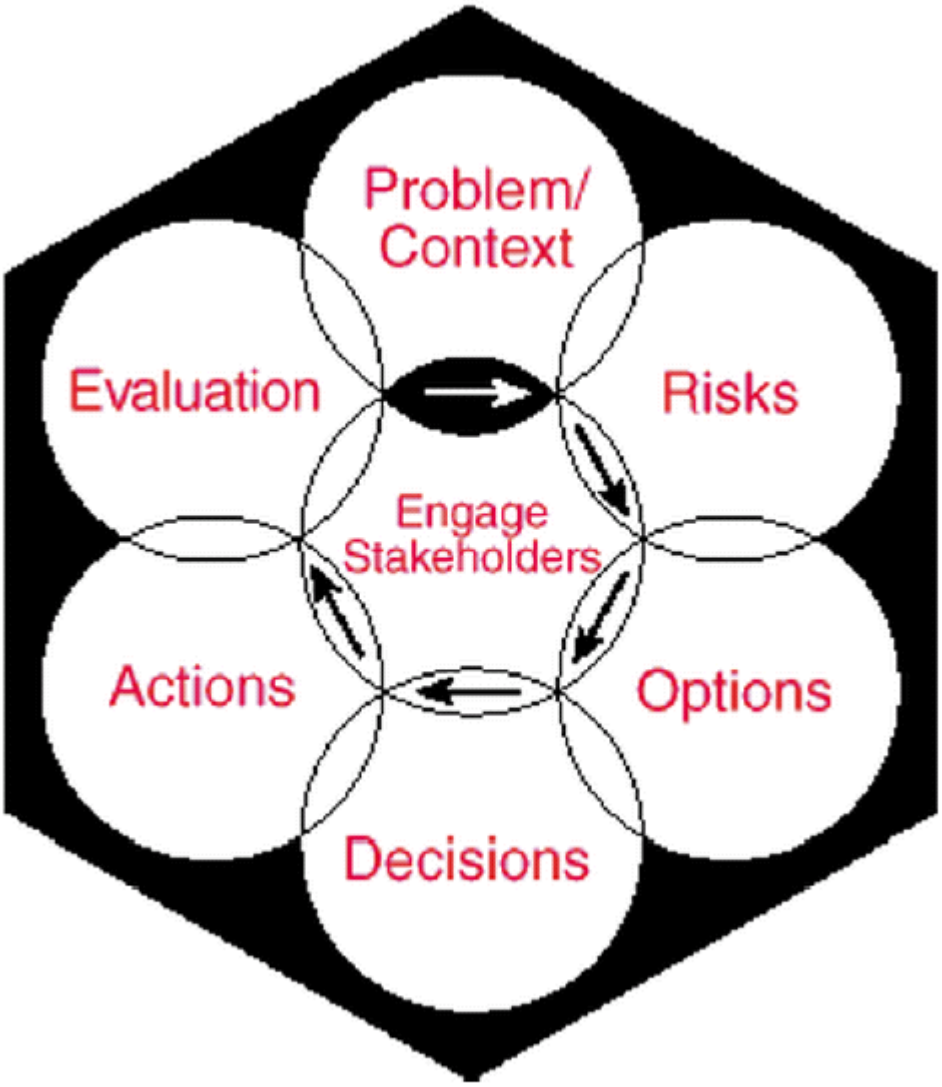
The ultimate purpose is essentially practical, namely to set limits on exposure to a hazard so that the likelihood of the resultant harm is acceptable in a regulatory context. If there is little model uncertainty (the hazard – harm or dose-response relationship is well characterised) and there is little data uncertainty, establishing acceptable exposure limits is straightforward. Where uncertainties abound, precautions may be taken. The nature and extent of those precautions are where the differences among different jurisdictions may become apparent.

1.2 Risk Management (RM)

Risk management is the process of deciding what appropriate actions to take in order to avoid, reduce, or eliminate a risk when there is (or might be) one. The results of a RA can provide some qualitative and quantitative information about the nature, severity, and likelihood of a risk, but it does not dictate the appropriate risk management response. RA may provide information useful for risk management decision-making, particularly in the context of regulatory policy, but the eventual risk management response also depends on many social, economic, legal, and other variables. The RA is necessary but not sufficient for regulatory action. The US Presidential/Congressional Commission on Risk Assessment and Risk Management proposed a risk management framework that illustrates how the risk assessment stage of RM is part of a decision-making continuum, guided by RM goals and providing information that feeds into the following stages (Figure 2). The framework emphasises the importance of defining a risk problem and the goals of RM prior to designing and conducting a RA (US Risk Commission 1997).

The US National Academy of Sciences report *Understanding Risk* (US NAS/NRC 1996) describes RA as "*. . . a decision-driven activity, directed toward informing choices and solving problems . . . The purpose of risk [assessment] is to enhance practical understanding and to illuminate practical choices.*" In other words, RA exists at the pleasure of RM. If a RA does not provide information that is useful to the risk manager in terms of deciding whether and how to manage a population's or individual's risks, then the RA has little utility.

Figure 2: Risk Management Decision-Making Framework



So while RA and RM may be distinct activities, risk management problems and goals should guide how risk assessments are performed and the questions they seek to answer.

One approach to RM is to establish regulatory standards to control the risk in question. Regulatory standards may consist of exposure limits (e.g., the maximum allowed concentration of a specified chemical in potable water), process requirements (e.g., the requirement to use Best Available Technology to limit pollutant releases), or complete bans

on products or processes. The aim of regulatory standards is to protect human health, organisations, or the environment from a particular risk to an agreed level of safety: That is, to put in place regulations that will reduce the likelihood of a potential harm to a level considered insignificant or negligible. Other, non-regulatory approaches to RM are also possible, such as voluntary substitution of less hazardous technologies or materials in manufacturing, providing tax incentives to encourage implementation of cleaner technologies, recycling and purchasing products that use recycled materials by communities and individuals, and upgrading sewage and municipal solid waste treatment facilities.

The choice of RM actions is dependant in part on scientific knowledge (the *a posteriori* facts) sufficient to determine the relationship between the hazard exposure and the harm realisation to some agreed confidence level (say 95%). If this relationship is not understood with confidence but there remains some evidence of a possible causal link (say on the balance of probabilities, i.e. greater than 50% confidence) then any RM actions may be considered precautionary in nature. In such cases the interface of RA and RM is mediated through precaution, i.e. it is prospective in nature (acting in advance of a clearly demonstrated risk). This makes the approach post-modern in many respects (De Marchi and Ravetz 1998, and de Sadeleer 2002) – particularly perhaps in the European regulatory context.

2 The EU Approach to Precaution and the Precautionary Principle (PP)

The Precautionary Principal became part of European Law in 1992 when the Treaty on European Union (the Maastricht Treaty) modified Article 130r of the Treaty establishing the European Economic Community to include the phrase "*Community policy on the environment… shall be based on the precautionary principle and . . "*. (EU 1999) (Article 174, ex 130r).

The PP is an integral part of EU primary law (EU 1999). However, Article 174 does not define the PP. Consequently, in order to clarify the situation regarding the correct application of the PP, the European Commission (EC) issued a Communication on the PP in February 2000 (EC 2000a).

The keystone of the Communication is that the PP gives permission to act under scientific uncertainty: "*To act or not to act*" as the Communication puts it (EC 2000a, p. 13). This permissory rule is in accord with principle 15 of the "*Rio Declaration*" from the 1992 UN Conference on the Environment and Development: "*In order to protect the environment,*

the precautionary approach should be widely applied by States according to their capabilities. 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".

For the EU, recourse to the PP presupposes that potentially dangerous effects deriving from a phenomenon, product, or process, i.e. the hazard, have been identified, and that scientific evaluation does not allow the risk, i.e. the degree or likelihood of harm, to be determined with sufficient certainty. If this is the case, then the implementation of an approach to RM based on the PP should be underpinned by a scientific evaluation, as complete as possible, that characterizes the degree of scientific uncertainty where feasible.

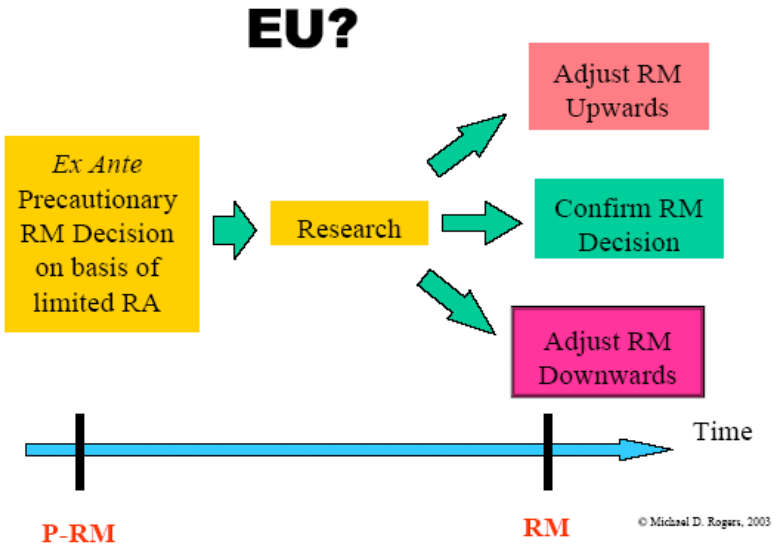
The most important aspect of the Communication concerns the criteria by which the resulting precautionary actions (PA) should be judged (having invoked the PP). These (five) criteria are as follows:

1. The PAs should be *proportional* to the chosen level of protection.
2. The PAs should be *non-discriminatory* in their application.
3. They should be *consistent* with similar measures that have been previously taken.
4. The PAs should be *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).
5. They should be *subject to review*, in the light of new scientific data. (Furthermore, the PAs may include *assigning responsibility for producing the scientific evidence* necessary for a more comprehensive risk assessment [Section 6.4 of the Communication].)

The fifth principle, namely that the PAs should be *subject to review* in the light of new scientific data, is the only principle that directly relates to the PP. It ensures that measures based on the PP should be maintained only so long as scientific information is incomplete or inconclusive, and that the possible risk is still considered too high to be imposed on society, in view of the chosen level of protection. Consequently, measures should be reviewed periodically in the light of scientific progress and amended as necessary (see Figure 3).

The Communication on the PP was broadly endorsed by the European Council at its 2000 meeting in Nice (European Council, 2000). It was also endorsed by the European Parliament (European Parliament, 2000, Article 11 *et seq.*). Furthermore the Communication

Figure 3: Precautionary RM in the EU?



has been recognised by the European Court of Justice in a number of cases (de Sadeleer 2002).

The Precautionary Principle has now been explicitly incorporated into EU secondary law in a number of Directives and Regulations. It is a core element of the EU's General Food Law (Regulation 178/2002) and of the EU's GMO law (Directive 2001/18, see for example Rogers 2004). This body of primary law (the Treaties), secondary law (Directives, Regulations, etc.) and what might be termed "soft law" (such as the Communication on the Precautionary Principle) is being interpreted by the European Court of Justice in its case law.

A useful example of the operation of Figure 3 in practice, concerns the precautionary risk management of phthalates, which are a group of chemicals widely used to soften normally-rigid PVC. The resultant material is used in the manufacture of a range of products from soft toys to medical equipment. Studies have shown that some phthalates can produce liver and kidney damage in laboratory animals (SCTEE 1998). Furthermore, simple experiments have indicated that the phthalates could be leached out of the PVC by prolonged exposure to saliva (SCTEE 1998). Consequently, the European Commission took

precautionary action to mitigate the postulated risk that children might be absorbing damaging quantities of phthalates from such toys. This action was promulgated in Decision (99/815/EEC) of 7 December 1999 prohibiting the placing on the market of toys and childcare articles intended to be placed in the mouth by children under three years of age made of soft PVC containing one or more of certain specified phthalates (European Commission 1999). The Commission had previously requested the Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTEE) for an opinion on the risk from phthalates in toys and this was delivered on 27 November 1998 (SCTEE 1998). The Committee confirmed that there were grounds for concern with potentially low safety margins concerning the exposure of children to certain phthalates in connection with their use in soft PVC toys (liver and kidney and testicular damage).

The Decision was adopted on the basis of Article 9 of Directive 92/59/EEC on General Product Safety which gives the Commission the power, under specified conditions, to adopt decisions that require the Member States to take measures in respect of products posing serious and immediate risks. Such measures are temporary (usual validity 3 months) and this particular Decision has been extended 18 times. Now that a full risk assessment has been carried out (SCTEE 2001), and in the light of more recent scientific data, permanent measures have been proposed to Parliament and Council. It should be noted that the ban was temporary (pending more information); that it was specific to certain products (soft toys); and that it was taken in parallel with research actions to make the risk assessment more quantitative. Finally, the precautionary action is to be replaced by a permanent RM decision (EC 2004). This accords, more or less, with the decision process illustrated in Figure 3.

A second example illustrating the dynamic of scientific knowledge and the impact of this dynamic on the risk management process concerns BST. BST or bovine somatatropin is a hormone that controls lactation in cows. For some years BST has been commercially produced as an agricultural pharmaceutical using red biotechnology (rBST) to boost milk production. The US FDA approved the use of rBST in 1993 (see Chapter 4). However, the use of rBST was banned for ten years in Europe in 1990 as a precautionary measure (European Council 1990) except for the purposes of carrying out scientific and technical trials. The risk related reason for this prohibition was that the various possible adverse effects of substances like BST were not sufficiently clear and that a period of time should be provided for in-depth studies. Plausible risk scenarios were postulated, both in terms of animal and human health,

and thus the ban was limited to the time required to obtain further information on these risk scenarios.

This prohibition was made permanent in 1999 and the exception that had been available for scientific and technical trials was removed (European Council 1999). This second and final decision was based on research that had demonstrated that injecting rBST increased the risk of mastitis in cattle and increased the duration of necessary treatment for the affliction. Furthermore, there were increases in foot and leg disorders in dairy cattle when rBST was administered, together with severe reactions at the injection site. Thus for animal welfare reasons, which were required under The European Convention for the Protection of Animals Kept for Farming Purposes, the prohibition was made permanent. Precautionary action under scientific and technical uncertainty (the time-limited prohibition of 1990) had been replaced by a risk management decision based on new knowledge.

These two examples relate strictly to the fifth criteria concerning precautionary actions and thus may be compared with the US leaded petrol case described in the following section. However, other precautionary actions are also taken to account for model deficiencies, such as safety factors, linear extrapolation of dose - effect curves to low exposures (as with carcinogenic hazards).

3 The US approach to precaution

In contrast to the EU, the US has not explicitly embraced the PP in legislation or regulation. It is often the case, however, that US regulatory agencies decide on a course of action to protect public health, safety, or the environment before science has resolved all the key factual questions about a suspected hazard and the effectiveness of prevention or mitigation efforts (US OMB 2003). Different approaches to RA and RM are taken by different US regulatory agencies depending on their statutory mandates and regulatory goals.

To a large extent, the body of US statutory law that seeks to ensure public health, safety, and environmental quality—or at least mitigate risks to health and the environment—was established before quantitative RA was a well-recognized and codified discipline. Most of the methodology of RA was developed in reaction to the calls by these laws to define limits on potential risks such as chemical exposures, for example, that will protect the public health "*with an adequate margin of safety*" [42 U.S.C. §7409(b)(1) (Clean Air Act)] or similar precautionary language. That is, in passing the laws, the US Congress called on the regulatory

agencies to develop means to assess risks so as to make RM choices that would achieve the stated qualitative goals of health or environmental protection (Rhomberg 1997).

Although the PP has not been embraced in the US as an explicit basis for regulation, it has guided US regulatory RM decision-making for many years (Charnley and Elliott 2002). For example, in the 1950s the Delaney Clause required the Food and Drug Administration to ban outright food and colour additives that had been shown to produce tumours in humans or laboratory animals, whether or not they posed a risk to public health [Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A.§§409(c)(3)(A), 706(b)(5)(B), and 512(d)(1)(H)]. In the 1970s, a legal basis for a US precautionary approach was established by the *Ethyl Corp. v. U.S. Environmental Protection Agency* decision [541 F.2d 1, 6 ELR 20267 (D.C. Cir.), cert. denied, 426 U.S. 941 (1976)], which involved the ban of leaded gasoline. At the time there was great debate about the wisdom of taking such a radical step when the benefits of doing so were unclear. But the US Court of Appeals for the DC Circuit upheld the US Environmental Protection Agency's (EPA's) decision to take a precautionary approach and ban leaded gasoline anyway, even in the absence of scientific evidence adequate to demonstrate exactly what the risks from the lead were or what the benefits of removing it would be. As it turned out, banning leaded gasoline was the single most important contributor to the virtual elimination of lead from air and from most children's blood. Today only 1.6% of US children aged 1-5 years have blood lead levels equal to or above the level associated with learning deficits, 10 μg/decilitre blood, compared to 4.4% in the early 1990s (US CDC 2005); in 1976 the mean lead level for the US population was 12.8 μg/decilitre blood (ATSDR 1999).

In 1980, however, the US Supreme Court's *Benzene* decision turned away from the precautionary policy of the *Ethyl* decision and substituted a fact-based principle focusing on the extent of risk [448 U.S. at 607]. The *Benzene* decision struck down a workplace standard for benzene exposure that was based on a policy of trying to reduce concentrations of benzene as far as technologically possible without considering whether existing concentrations posed a "significant risk" to health. The Supreme Court decided that benzene could be regulated only if it posed a "*significant risk of material health impairment*". Although the Court did not define "*significant risk of material health impairment*" and stressed that the magnitude of the risk need not be determined precisely, the decision strongly implied that some form of quantitative RA is necessary as a basis for deciding if a risk is large enough to deserve regulation.

Relying on quantitative RA for scientific input to RM does not imply that precautionary

considerations are excluded. Precaution plays a role in both RA methods and RM decisions in the US, with decision-makers relying on a number of different science-based precautionary approaches in assessing risks and taking protective regulatory actions (US OMB 2003). In the case of chemical exposures, for example, the US EPA builds in conservative, precautionary measures by relying on assumptions about maximum exposures, choosing the most sensitive laboratory animal species and effect to represent human sensitivity, and using statistical upper bounds instead of maximum likelihood estimates of risk. In the interest of precaution, uncertainties about interspecies and inter-individual variations in sensitivity to toxicity are compensated for through the use of uncertainty factors and safety factors to lower exposure limits. Such measures are meant to protect the most sensitive segments of an exposed population, where sensitivity may be attributed to either greater exposure or greater susceptibility to toxicity than the average individual. The US EPA has issued extensive guidance for assessing chemical risks, which has recently been summarised and critically evaluated (US NAS/NRC 2005).

Regulation of hazardous air pollutants (HAPs) under the 1990 amendments to the Clean Air Act provides an example of how the PP has been implicitly incorporated into federal environmental legislation (Goldstein and Carruth 2003). After 18 years of relying on a procedurally cumbersome, risk-based approach to setting standards limiting air pollutant concentrations, EPA had promulgated standards for only 7 substances. In response, Congress passed amendments requiring a technology-based approach to limiting pollutant emissions regardless of the degree of risk and enumerating 189 substances that Congress considered hazardous, substituting legislative fiat for RA. By focusing attention on all HAPs regardless of risk, by measuring success in terms of tons of pollutants, not risk, reduced, and by mandating particular technologies, a focus on the most toxic pollutants is lost, potential impacts on public health cannot be assessed, and incentives to develop better technologies are eliminated (Goldstein and Carruth 2003). The Clean Air Act is thus an example of how purely risk-based or purely precautionary approaches to limiting risks may not achieve the intended goal of public health protection.

Food safety in the US is ensured in part by putting the precautionary burden of guaranteeing safety onto food processors through strict liability and through regulation, so that a processor who sells a food that causes injury to a consumer is legally responsible even in the prior absence of actual knowledge of the hazard. Like the US EPA, the US Food and Drug Administration (FDA) incorporates precaution by employing conservative, health-

protective assumptions and safety factors when assessing potential risks from, for example, food additives, food-borne pathogens, or chemical contaminants. For example, FDA's Pathogen Reduction/Hazard Analysis and Critical Control Points (HACCP) regulation relies on risk-based precaution to prevent food-borne illness by placing the burden on industry to produce safe food and on FDA to ensure industry meets its burden. Regulation of food additives also puts the onus of demonstrating safety on industry and uses safety factors to determine acceptable dietary exposure levels for individual substances.

The US Department of Agriculture (USDA) also uses both risk assessment and precaution to ensure food safety. Importation of cattle from Canada was banned recently as a precautionary measure against potential BSE transmission when BSE-contaminated cattle were found there; the ban was lifted when the risk of letting BSE-infected cattle into the US was characterised qualitatively as "low".

Disposal of low-activity nuclear waste in the US is an area that is not guided by RA and is considered inadequately protective in some instances and unduly stringent in others (US NAS/NRC 2003). Although US statutory and institutional authority to ensure the safe management of such wastes is adequate, RM relies on a complex and confusing patchwork of regulations based on the origin of the waste and not on its risk. Disposal is regulated by at least 12 statutes and several different agencies, with precautionary approaches employed in some cases and not in others.

Thus, in general, the US links precautionary and quantitative approaches to regulatory RM in order to fulfil both the qualitative goals of Congressional statutes and the legal implications of judicial decisions such as *Benzene*. Because science is generally uncertain or incomplete, purely risk-based approaches are infeasible and precautionary measures, such as protective assumptions or safety factors, are included to help guide RM decisions. Finding the appropriate balance between risk and precaution continues to be a challenge.

4 Concluding Comments

Debates about the nature and extent of precaution associated with European and US risk assessment practices often centre on when the science available to characterise a particular risk is adequate and, consequently, on how much precaution is needed to assure public health and environmental protection. The difference between science and regulatory science can be an important one. Although science informs risk assessment practices, when there are several

possible interpretations of the science, the more precautionary choice is assumed to be appropriate for regulatory purposes, if not necessarily correct. Scientists and regulated parties often believe that the weight of the scientific evidence supports a different choice, but agencies mandated to protect health and the environment may believe that uncertainty about the science justifies precaution nonetheless. Scientists and regulated parties also criticize agency risk assessors for confusing risk assessment and risk management. By making conservative assumptions and precautionary choices as part of the risk assessment process, risk assessors are de facto acting within the realm of risk management, thought to be the provenance solely of risk managers with greater public accountability. While it is true that making precautionary choices and assumptions as part of risk assessment does constitute risk management to some degree, it is impractical---and perhaps impossible---to completely disaggregate the two. The solution is to characterise and articulate clearly the nature and extent of relevant uncertainties and to make each corresponding precautionary assumption and its underlying justification or rationale as transparent as possible. Such transparency improves accountability and highlights areas where further research to reduce particular uncertainties may have the greatest impact on the outcome of a risk assessment.

The preceding sections indicate that there are many similarities between the approach to risk regulation in the EU and the US. Acting before the consequences of a particular risk scenario are fully understood is accepted on both sides of the Atlantic. The EU and US also have parallel approaches for taking account of model deficiencies and uncertainties by means of safety factors, etc. Where there are differences these are not due to conflicting philosophies but to case-by-case differences in emphasis, as the earlier chapters have illustrated. Differences may also be attributable in some cases to the different legal traditions found in the US and EU, as Chapter XX illustrates.

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