

Risk & Remediation

International Risk Policy

Differences in the U.S. and EU regulatory systems make wholesale translation of policies problematic.

Historically, the United States has been the leader in the development of environmental programs. In the U.S., this typically has involved discretely defined programs addressing chemicals either in individual media or specific environments (e.g., the workplace), or in specific chemical uses (e.g., pesticides). Over the past decade, the world has seen the globalization of environmental concerns and risk reduction approaches, as reflected in the 1992 Rio Declaration and the 1997 Kyoto Protocol (see figure). In recent years, other countries, in particular the European Union (EU) members, are taking action prior to the U.S. For example, Sweden has decided, with limited exceptions, to ban the use of cadmium in plastics. However, when comparing environmental policies, it is important to recognize the fundamental social, legislative,

Overall, environmental policy making in the EU member countries may be characterized as less formal, more flexible, and less analytical than environmental policy making in the U.S.

and judicial differences that exist between the U.S. and the EU countries. These differences, as summarized in the following paragraphs, militate against the wholesale adoption by the U.S. of specific policies developed by other countries.

The regulatory system of the U.S. involves a dynamic between relatively specific environmental statutes, a strong judiciary, and a litigious society. Agency discretion may be limited by the requirements of the empowering legislation, as many of the specific risk-based elements of a particular program may be prescribed in the legislation itself (e.g., 10^{-6} to 10^{-4} risk range in CERCLA). Moreover, the implementing regulations that the U.S. EPA must develop are further supported by in-depth scientific and risk-based analyses. As an example, consider the recent arsenic maximum contaminant level (MCL) proposed in January 2001 by the EPA, which was recently withdrawn. The *Federal Register* documentation for this proposal contained nearly one hundred pages of text, including a risk analysis for different tumor sites, a cost-benefit analysis, and specific details on analytical methods for arsenic (U.S. EPA, 2001). As a consequence of this specificity, there is usually limited interpretation of

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Letter to our Readers

May 2001


Dear Colleague,

Despite increasing globalization of our economy, regulation of chemicals remains distinct by country. In this issue of *Trends*, we focus on international risk issues that potentially affect U.S. industries with international operations. We compare and contrast regulatory systems between the U.S. and the European Union, consider various interpretations of the Precautionary Principle, and examine the alternative classification methods for carcinogenic compounds used by various organizations and in various countries.

Contributors to this issue include Dr. Barbara Beck, Gradient Principal and internationally recognized expert in toxicology and health risk assessment. Joining her are Dr. Mara Seeley, a Gradient toxicologist, and Dr. Lorenz Rhomberg, a Gradient Principal and quantitative risk assessment expert. Finally, we welcome Ms. Cynthia Sonich-Mullin, Environmental Health Scientist at the U.S. EPA National Center for Environmental Assessment, who spent three years at the World Health Organization developing their Harmonization Project. Ms. Sonich-Mullin shares her thoughts on the EPA's role in the international risk assessment community.

We hope this issue of *Trends* will provide you with new perspectives on various international approaches to chemical risk management.

Yours truly,



Neil Shifrin
President

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International Risk Policy

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these laws and regulations on the part of the EPA. But, judicial interpretation of environmental statutes often occurs as a consequence of litigation involving challenges to or demands for environmental regulations. Court decisions may result in the setting of timetables for agency action or setting aside an agency decision, as in the recent overturning of the proposed MCL for chloroform.

In contrast, the EU political system in the member countries is based upon a civil code with member-country governments responsible for implementing and administering EU directives. Member countries have wide latitude regarding the implementation of these directives, which regulators can interpret and enforce as appropriate for their individual country (Borchardt, 2000). In addition, the judiciary is relatively weak in contrast to the U.S. judiciary. Individuals or organizations do not sue governments as frequently regarding the implementation (or lack of implementation) of environmental statutes, as in the U.S. Overall, environmental policy making in the EU member countries may be characterized as less formal, more flexible, and less analytical than environmental policy making in the U.S. Given this understanding of the differences between the U.S. and EU systems of governance, one can appreciate the potential pitfalls of the wholesale adoption of EU proposals in the U.S.

Of particular interest in this regard is the recent EU Commission White Paper, "Strategy for a Future Chemicals Policy" (Commission of the European Communities, 2001). The objectives of the White Paper are broadly stated, and emphasize protection of human health and the environment, while maintaining the competitiveness of the EU chemical industry. The White Paper proposes an enhanced testing program for new and existing chemicals, with promotion of non-animal test methods as key to achieving these objectives. In addition, a registration, evaluation, and authorization (called REACH) system is proposed. The Precautionary Principle (see related article) is strongly embedded in the White Paper. EU members would be responsible for

enforcement in their own countries. The approaches in the White Paper are largely hazard-based. For example, there is an emphasis on labeling and restriction as control measures based solely on chemical characteristics (*e.g.*, carcinogenicity). Broadly speaking, it is difficult to directly apply the concepts of the White Paper to environmental policies of the United States, because the hazard-based analyses and approaches of the White Paper are in contrast to the long-established risk-based approaches and cost-benefit analyses used in the U.S. for development of regulations.

While benefits may accrue in the international sharing of underlying toxicity information or development of test methods, cross-country application of such information to environmental policy must be approached with great caution. Efforts to "import" international regulatory constructs into the U.S. system must be careful to not undermine the use of risk-based policy development, and to not result in a detrimental impact on trade and U.S. competitiveness.

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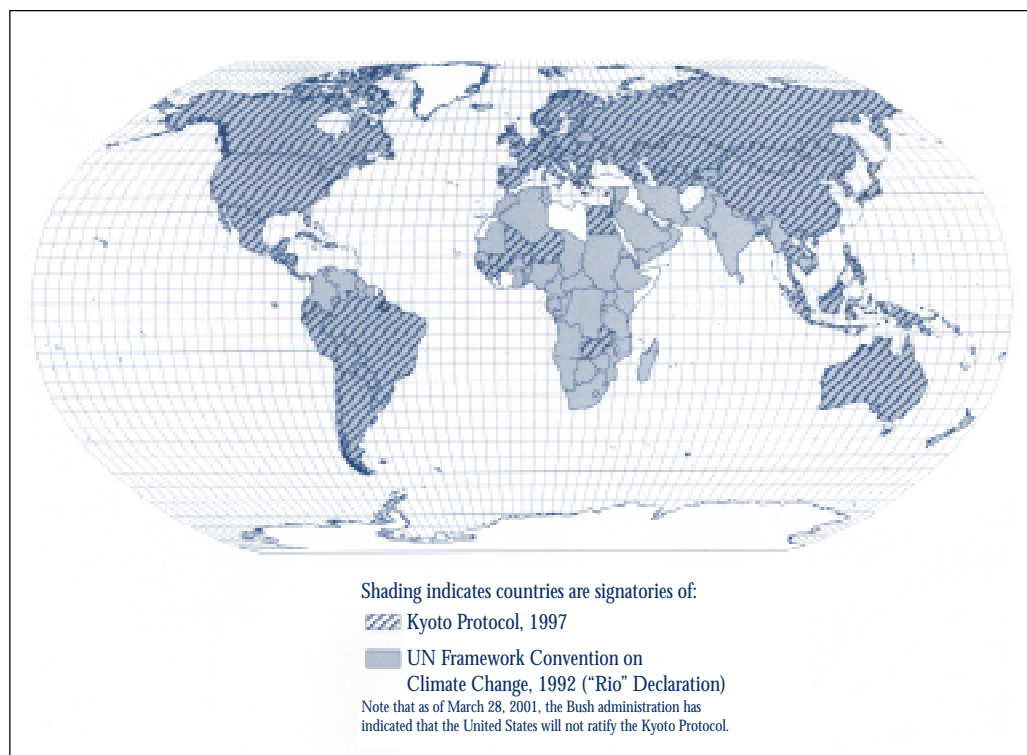
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Carcinogen Classification

Differences in carcinogen classification schemes vary dramatically among different countries.

Although much of the public may assume that classification of a chemical as cancer-causing is a standardized and straightforward process, in fact, countries and organizations have different

These differences in carcinogen classification have important implications for a range of risk management activities in individual countries...

classification schemes that can yield different results. These differences in carcinogen classification have important implications for a range of risk management activities in individual countries, including setting

Occupational Exposure Levels (OELs), labeling, and establishing use restrictions. These differences preclude selection of a single system for carcinogen classification for all countries. This article presents some of the key features of different classification systems in European countries and how they are applied for purposes of risk management.

The International Agency for Research on Cancer (IARC), which was the first organization to develop a classification scheme, classifies chemicals according to carcinogenic potential in humans, as do the European Union (EU), Germany, and Sweden (Beck *et al.*, 2000; IARC, 2001). That is, these systems rank carcinogens according to their likelihood of being a human carcinogen; chemicals known to cause cancer in humans receive the highest rating. In contrast, the Netherlands and Norway don't explicitly differentiate between animal and human carcinogens. The Netherlands classifies carcinogens according to genotoxicity and Norway classifies carcinogens according to potency.

These classification schemes have direct relevance to certain risk management activities, such as setting OELs. OELs for genotoxic carcinogens (*i.e.*, those that cause DNA damage) are often based on technological feasibility, and tend to be legally binding. OELs for non-carcinogenic and non-genotoxic carcinogens are more often risk-based, and are considered guidance values. Interestingly, the Norwegian system is not used in setting OELs, but solely for labeling and establishing use restrictions (Beck *et al.*, 2000).

A review of carcinogen classification for a selection of chemicals indicates there is general agreement for carcinogen classifications based mostly on human data (*e.g.*, benzene and vinyl chloride). There is less agreement for classifications that are based primarily on animal data (*e.g.*, tetrachloroethylene and trichloroethylene). For the chemicals reviewed, there is a concordance in classification between the EU, Germany, and Sweden. However, IARC, whose classification system is similar

to that of the EU, Germany, and Sweden, is more likely to classify chemicals as having a greater carcinogenic potential in humans (*e.g.*, cadmium, ethylene oxide, tetrachloroethylene, and trichloroethylene).

The reasons for different classifications of the same chemical are varied. One is choice of underlying data. Germany considers data from malignant tumors only, whereas other countries, such as Norway, consider data from both malignant and benign tumors. The Netherlands consider data from chronic bioassays, mutagenicity tests, as well as other data (*e.g.*, enzyme inhibition or induction) (HCN, 1996; Moolenaar, 1994; Beck *et al.*, 2000). Differences in classification also can arise due to differences in consideration of mechanisms, biotransformation, toxicokinetics, and choice of data sets. For example, IARC relies solely on published data, whereas other countries, such as Norway, review both published and unpublished data. Differences can also arise due to the intended purpose of classification. For example, while most countries classify chemicals to estimate risks and set OELs, Norway classifies chemicals for labeling and establishing use restrictions, *e.g.*, the amount of substance allowed in a consumer product.

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CLASSIFICATIONS FOR SPECIFIC CARCINOGENS IN VARIOUS EUROPEAN COUNTRIES AND SCIENTIFIC ORGANIZATIONS

Chemical	European				
	IARC	Union	Germany	Netherlands	Norway
Acrylonitrile	2B	n.c.	2	I	K2
Benzene	1	1	1	I	K2
Cadmium	1	2	2	II	II
Ethylene oxide	1	2	2	I	K1
Tetrachloroethylene	2A	3	3	II	K2
Trichloroethylene	2A	3	3	II	K3
Vinyl chloride	1	1	1	I	K2

While there is consensus on the classification of benzene and vinyl chloride, there is less agreement on the other chemicals.

Nomenclature

IARC: 1 – Carcinogenic to humans; 2A – Probably carcinogenic to humans; 2B – Possibly carcinogenic to humans

EU: 1 – Substances known to be carcinogenic to humans; 2 – Substances which should be regarded as if they are carcinogenic to humans; 3 – Not classifiable as to carcinogenicity, but is of concern to humans owing to possible carcinogenic effects

Germany: 1 – Carcinogenic to humans; 2 – Carcinogenic in animal studies; 3 – Suspected carcinogenic potential

Netherlands: I – Genotoxic carcinogens; II – Non-genotoxic carcinogens

Norway: K1 – High potency animal and human carcinogens (TDx, the lowest dose in a chronic animal bioassay causing tumors, is 1 – 15 mg/kg-day); K2 – Medium potency animal and human carcinogens (TDx of 15 – 600 mg/kg-day); K3 – Low potency animal and human carcinogens (TDx greater than 600 mg/kg-day); II – Limited data available for classification

n.c.: Not classified

Parsing the Precautionary Principle

Various renderings of the Precautionary Principle have led to confusion in its proper application.

For several decades, environmental protection has included the tenet that we need not know with scientific certainty that an agent or activity causes harmful effects before taking prudent action to limit or avoid exposure. In recent years, a formal elaboration of this idea – named the Precautionary Principle – has been proposed as an overarching paradigm for risk management decision-making. Versions of it are increasingly being incorporated as a guiding principle in international trade and environmental agreements, in the regulatory program of the European Community, and in some national laws, chiefly in Europe. A key

Given the wide acceptance of the notion that prudence in the face of uncertainty is sound public policy, why has the Precautionary Principle proved so controversial?

event was an articulation of the principle in the 1992 Rio Declaration on environment and development (see box), which states that scientific uncertainty about potential but undemonstrated serious

risks is not a reason to delay appropriate action to avoid them.

Given the wide acceptance of the notion that prudence in the face of uncertainty is sound public policy, why has the Precautionary Principle proved so controversial? And why, in view of the “err-on-the-safe-side” approaches that have long been used in assessing and controlling potential health risks from environmental chemicals, is the principle seen by some as a new, and even revolutionary, paradigm shift in environmental protection? The answers lie in the widespread disagreement about what the Precautionary Principle really calls on the risk management process to do, and to what degree it should supersede a fully developed risk analysis.

Consider the subtly transformed version of the Principle in the 1998 Wingspread Statement: “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” (W. Alton Jones Foundation, 1998). In this phrasing, the Rio principle’s statement that uncertainty is no reason to delay action has been changed to imply that uncertainty *requires* action. It does not address how plausible, irreversible, or serious the threat must be, and it makes no mention of tailoring the precautionary action to be cost-effective or proportional to the risk entailed. Some of the most zealous advocates have interpreted the Precautionary Principle to mean that *no* activities or environmental releases should be permitted until they can be unconditionally “proved safe,” a practical impossibility before the fact.

The Rio Declaration’s version and the interpretation endorsed by the European Commission stress that a plausible possibility of serious or irreversible harm must be recognized (*i.e.*, there must be a substantial downside possibility that would be hard to catch until it is too late), and any precautionary actions should be cost-effective, appropriate, and proportionate to the uncertain threat being avoided. Moreover, precautionary actions are seen as provisional, with research being undertaken to better define whether feared risks are real. Far from obviating risk analysis, this approach embeds the precautionary ethos into a full analysis of potential risks and uncertainties, competing risks, tradeoffs, alternative actions, and feasibility to arrive at a well-considered risk management strategy. Its chief departure from previous approaches is to emphasize before-the-fact thinking about potential modes of adverse effects that may arise, and to allow for our uncertainty and imperfect ability to predict them with confidence.

In this era of rapidly developing new technologies and globalization, an action that to one party is the exercise of the legitimate right of a government to protect its citizens from risks may seem to another to be mongering baseless fears as an excuse for illegitimate trade barriers. The Precautionary Principle can

“In order to protect the environment, the precautionary approach shall 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.”

Source: United Nations Conference on Environment and Development (UNCED). 1992. UNCED Principle 15, Final Declaration of the UN Conference on Environment and Development, Rio de Janeiro.

help to sort out such disagreements whenever it is viewed in its proper context – as a construct that helps to inform risk management decisions, rather than as a substitute for fundamental risk-based thinking.

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W. Alton Jones Foundation. 1998. Wingspread Statement on the Precautionary Principle. Finalized at the Wingspread Conference Center. Racine, Wisconsin. January 23-25.

What's New at Gradient

Rosalind Schoof Appointed to NRC Committee

Dr. Rosalind Schoof has been appointed to the newly formed National Research Council Committee on Risks from Toxicants and Pathogens in Biosolid Fertilizers. During the next 18 months, this committee is charged with reviewing information on the land application of sludge and evaluating the methods used by the U.S. EPA to assess risks from chemical pollutants and pathogens in sludge.

Lorenz Rhomberg Named to Expert Panel

Dr. Lorenz Rhomberg has been named to an expert panel to assess toxicity and possible health impacts from exposure to the endocrine-active chemical Bisphenol A. The panel is being convened by the Harvard Center for Risk Analysis in association with the Society of Plastics Industry.

Tom Lewandowski Wins Award

Tom Lewandowski and co-authors S.M. Bartell, R.A. Ponce, and E.M. Faustman were among the winners of the Society of Toxicology's Best Abstract Award for their abstract titled, "Mechanism-Based Comparison of *In Vitro* and *In Vivo* Data on Methylmercury Toxicity in Developing Rodents." To view this abstract, please see the SOT website at www.toxicology.org, or email trends@gradientcorp.com.

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Recent and Upcoming Presentations

Newark, NJ. June 1. Barbara D. Beck. "Use of Human Data in Evaluating Adult/Child Differences: Examples Using the Criteria Air Pollutants," presentation at the 5th Annual 10X Workshop on Evaluation of Default Safety Factors in Health Risk Assessment.

Newark, NJ. June 1. Lorenz Rhomberg. "Use of Pharmacokinetics, Dose Scaling, and Empirical Descriptions of Uncertainty in Extrapolation across Age Groups," presentation at the 5th Annual 10X Workshop on Evaluation of Default Safety Factors in Health Risk Assessment.

Recent Articles

Beck, B.D., T.M. Slayton, E.J. Calabrese, L. Baldwin, and R. Rudel. 2001. Chapter 2: The use of toxicology in the regulatory process. *Principles and Methods of Toxicology, Fourth Edition*. (Ed: Hayes, A.W.), Taylor & Francis, Philadelphia, PA, pp. 23-75.

Beck, B.D. and H.J. Clewell, III. 2001. Uncertainty/safety factors in health risk assessment: opportunities for improvement. *Human & Ecol. Risk Assessment* 7(1): 203-207.

Slikker, W., B.D. Beck, W.K. Anger, D. Bellinger, D.A. Cory-Slechta, and M.G. Paule. 2000. Cognitive tests: interpretation for neurotoxicity? *Toxicological Sciences* 58:222-234.

Brilis, G.M., J.C. Worthington, and A.D. Wait. 2001. Quality science in the courtroom: U.S. EPA data quality and peer review policies and procedures compared to the Daubert factors. *Environmental Forensics* 1:197-203.

Carcinogen Classification

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Thus, efforts to harmonize carcinogen classification among countries in Europe are premature. Nonetheless, agreement upon common data sets and other underlying issues (*e.g.*, guidance for considering benign tumors) would represent an important step forward.

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T R E N D S • I N

Risk & Remediation

Guest Editorial: The U.S. EPA's Role in International Harmonization of Risk Assessment¹

Recent advances in developing a "common language" for risk assessment make international sharing of data and approaches possible.

Is international harmonization of risk assessment a useful goal? You bet! The U.S. EPA has a thirty year history using a risk assessment approach to environmental protection. As the use of this approach increased globally, the EPA has shared information and collaborated to improve the science of risk assessment. Much has been learned, and there is much more to learn from and share with our international colleagues. Risk assessment methods must evolve to benefit from scientific advances. Revised and new tools provide the means to incorporate new information into assessments. As a leader in risk assessment, the EPA has worked toward improvement of methods and the development of innovative approaches. Harmonization plays an important role in this process.

In the context of risk assessment, harmonization is about compatibility. The goal is to bring assessment methods and approaches in accordance with one another on a global level.

What is "harmonization?" In the context of risk assessment, harmonization is about compatibility. The goal is to bring assessment methods and approaches in accordance with one another on a global level. This will result in a

number of benefits including increased confidence in the assessment process. The foundation of harmonization is sound science. Scientific discussions will result in the development of common assessment tools and increased understanding, improving our ability to interpret scientific data and incorporate it into the risk assessment process. However, until recently, a common risk assessment "language" did not exist to allow such discussions.

In 1994, the International Programme on Chemical Safety (IPCS), World Health Organization, initiated a process to promote discussions of the application of scientific data and

information into risk assessment. The EPA was instrumental in helping to initiate and lead the project on behalf of IPCS and continues its commitment through active involvement. EPA scientists have made effective contributions to a number of accomplishments including promoting the use of common data sets, clarification and use of terminology, and developing frameworks. These products have improved scientific credibility and have been useful for environmental decision-making.

For example, within the IPCS harmonization project, EPA scientists participated in an expert workshop to discuss the incorporation of mechanistic data into cancer risk assessments. An internationally-accepted framework for evaluating a mode of action for chemical carcinogenesis was developed. This framework has been incorporated into the EPA's proposal to revise its Cancer Risk Assessment Guidelines. The effort resulted in increased awareness and understanding; for the EPA, it helped to strengthen national approaches through global harmonization.

Harmonization provides a forum for scientific exchange. It is not about doing things one way or agreeing on past approaches. Rather, it is about incorporating scientific advances into risk assessment and creating credible future approaches; working together, leading to benefits for all. To achieve success, it is incumbent upon scientists in all sectors to participate in harmonization. The EPA has been a dedicated and supportive member of the international effort towards harmonization of risk assessment and intends to continue to be an active partner in this important effort.

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¹ The views expressed in this commentary are those of the author and do not necessarily reflect the official policies of the U.S. Environmental Protection Agency. While EPA intends to continue to be an active partner in the harmonization effort, it should be acknowledged that the author does not represent the official views of the Agency.

In the next issue:

Power and Utility Risk Issues

Impact of Power Plant Air Emissions

Electromagnetic Fields: Fact vs. Fiction

Guest Editorial: The Power Crisis in California

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