Pure Appl. Chem., Vol. 75, Nos. 11–12, pp. 2515–2519, 2003.

Workshop 5.2

Precautionary principle and endocrine active substances*

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Abstract: The precautionary principle has been central to many of the debates concerning the appropriate approach to the threat posed by endocrine active substances (EASs). This newly emerging principle has been applied to issues as diverse as persistent organic pollutants and the European trade barrier on beef from hormone-treated cattle.

INTRODUCTION

There is growing interest in the precautionary principle as both a rationale and a legal mechanism for control of agents potentially harmful to the environment and to public health. Described below is an overview of certain of the aspects of the precautionary principle pertinent to the difficult issues posed by compounds with effects on the endocrine system [1].

One of the earliest major international statements of the precautionary principle was in the 1992 Rio Declaration: "Nations shall use the precautionary approach to protect the environment. Where there are threats of serious or irreversible damage, scientific uncertainty shall not be used to postpone cost-effective measures to prevent environmental degradation" [2].

The focus on protective action despite scientific uncertainty is central to the many formulations of the precautionary principle. More recent definitions have extended the precautionary principle to include protection of public health as well as the environment. In some cases, the definitions seem to lower the bar for action under the precautionary principle by not requiring the "serious or irreversible damage" or "cost-effectiveness" found in the Rio definition, e.g., the Wingspread statement [3].

Of note is that the European Community (EC) has recently published a major document on the precautionary principle in which it does not provide a definition, instead in essence calling for regulatory actions to be judged by the extent to which they have a precautionary impact [4]. This failure to define a term being advocated for use in international treaties has led to some cynicism among U.S. officials who tend to see the precautionary principle as an excuse for European trade protection [5], a point recognized by European Union Environmental Commissioner Wallstrom, who stated, "We do not spend our days in Brussels—as some might think—in Machiavellian plotting to apply precaution to the detriment of U.S. businesses" [6].

THE PRECAUTIONARY PRINCIPLE AND THE SAFETY OF BEEF FROM HORMONE-TREATED CATTLE

Part of the American cynicism about the precautionary principle stems from a trade dispute about beef from hormone-treated cattle in which endocrine effects are a central issue. The World Trade

*Report from a SCOPE/IUPAC project: Implication of Endocrine Active Substances for Human and Wildlife (J. Miyamoto and J. Burger, editors). Other reports are published in this issue, *Pure Appl. Chem.* **75**, 1617–2615 (2003).

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Organization (WTO) responded to a complaint by the United States and Canada that the EC was unfairly excluding beef derived from animals treated with growth hormone. The EC argued in part that the precautionary principle provided an adequate justification for their exclusion, that under this principle there was sufficient evidence of the possibility of an adverse health effect, including cancer, to ban importation of beef from hormone-treated animals without a formal risk assessment. This led the WTO to consider whether the precautionary principle was an established principle of law applicable to adjudication of international trade disputes. The WTO ruling against the EC's ban on beef from hormone-treated animals was also upheld by the WTO Appellate Body [7,8]. The WTO appeared to support standard risk assessment approaches and to reject the argument that the precautionary principle was a reasonable basis for trade barriers, at least at that time. But the ruling was complicated by a number of considerations. Among the other U.S. and Canadian arguments most pertinent to the present paper were that the EC was inconsistent in not having limits on the levels of residues of similar hormones present naturally in foods, that an EC scientific body previously evaluated the hormone residue issue and had not found significant evidence of risk, and that the Codex Alimentarius Commission failed to support the EC position on beef from hormone-treated cattle as being a consumer risk. In addition, the WTO seemed to agree with the U.S. and Canadian argument that a major reason for the EC allowing potentially carcinogenic growth-promoting antibiotics in swine but not potentially carcinogenic growth-promoting hormones in cattle was its surplus of beef but not pork products, i.e., it was a trade barrier, not a health issue.

THE PRECAUTIONARY PRINCIPLE, DISTRUST OF SCIENCE AND GOVERNMENT, RISK PERCEPTION, AND EASs

Increasing distrust of science and of government is cited as a reason for the acceptance of the precautionary principle. This is said to be particularly true for Europe where a series of incidents such as "mad cow disease" in Britain and unnecessary HIV in the hemophilia population in France have undermined public confidence in governmental science and health pronouncements. The preamble to the 2000 EC Communication on the Precautionary Principle states "The Communication recalls that a number of recent events have undermined the confidence of public opinion and consumers..." [4]. In the United States, frustration with the slow pace of science and risk-based regulation of hazardous air pollutants fostered changes in the regulation of hazardous air pollutants in the 1990 Clean Air Act Amendments that fit well under the precautionary principle. These include a shift in the burden of proof so that it is now necessary to demonstrate the safety of a chemical rather than its risk of harm, and a primary reliance on maximum available control technology rather than risk assessment as a regulatory control device. This distrust and frustration is understandable. All too often, industry and government have used scientific uncertainty as a means to delay unwanted but necessary regulation [9,10].

In the case concerning beef from hormone-treated animals, the European Community argued that the public's perception of the risk due to hormone residues in their food, separately from scientific factors, is a reasonable basis for banning this product. While in this case, the WTO appellate body appeared to implicitly reject the proposition that risk perception can substitute for or overcome scientific evidence of risk, a subsequent WTO appellate body ruling appears to have brought risk perception back into acceptability [11,12].

Environmental groups have been particularly active and effective in expressing concern about the potential harmfulness of EASs and have couched their concerns in the context of the precautionary principle. This perception of hormonal interactions as being a particularly dangerous problem worthy of precautionary action might well account for the rapid and widespread public acceptance of the purported marked synergistic effects of hormones [13], a finding that needed to be withdrawn after it could not be replicated. In essence, the public has been primed to expect that the endocrine system is particularly susceptible to environmental agents and that subtle effects in this system could have wide ranging health and environmental consequences. The extent to which this is true is the subject of much other

discussion within this volume. Whatever the case, the obvious danger in regulating on the basis of perception is that manipulation of perception is the stock in trade of both politicians and advertising managers, and such manipulation counters the potential value of scientific enquiry into the truth of these important issues.

THE PRECAUTIONARY PRINCIPLE, RISK ASSESSMENT, RISK MANAGEMENT, AND SCIENTIFIC RESEARCH

As a simplification, two types of actions can be discussed as falling under the precautionary principle: those that add additional levels of protection within standard risk assessment and risk management approaches (e.g., additional prudence in default assumptions, more stringent safety factors, and acceptable risk levels); and those that go beyond usual risk-based approaches (e.g., shifts in the burden of proof, actions based upon hazard without sufficient information to assign risk) [12]. Within the standard risk paradigm, a key issue for EASs that cause cancer at high doses through hormonal effects is whether they should be held to the standard conservative assumption that any single molecule of a carcinogen can cause cancer. This supposition is pertinent to issues concerning the mechanism by which hormonal agents produce cancer—a tumor-promoting effect would, at least to some, argue that a one-hit cancer causation model is inappropriate.

One of the concerns about the precautionary principle is that it will downgrade the value of research that in the long run could lead to definitive answers concerning the risk of EASs [14,15]. There are two reasons for this concern. Firstly, some advocates of the precautionary principle view risk science as antithetical to postmodern democracy and risk assessors as a technocracy at the beck and call of industrial interests [16]. Secondly, once an action has been taken under the precautionary principle, there appears to be a tendency for the research funding agency to look for new problems to study, rather than persist to find out if the precautionary action is justified. Invoking the precautionary principle by definition means that there is a finite probability that an erroneous action with significant societal and/or economic cost has been taken—if there were certainty, or the cost was minimal, there would be no need to invoke the precautionary principle. In fact, it is a truism that the more precautionary a society, the more likely it is to make costly mistakes [14]. Accordingly, the precautionary principle would seem to provide a major justification for basic mechanistic research and for research to discover if the precautionary action was in fact justified. It would be particularly problematic to erroneously take a precautionary action for a concern such as the disappearance of amphibian species, which has been ascribed to EASs, but not do the follow up research needed to discover if the action was erroneous as the effect on amphibians was due to some other factor. Unfortunately, the experience of a marked decline in support for hazardous air pollutant research following the passage of the 1990 U.S. Clean Air Act Amendments suggests that regulating on the basis of the precautionary principle may well interfere with obtaining the needed understanding to make appropriate decisions.

Another potential weakness of the use of the precautionary principle is also exemplified by EASs—the difficulty in assessing the potential for net positive trade-offs between the valuable and negative aspects of a situation. This has been central to the argument about genetically modified foods and malnutrition [17]. Similarly, agents capable of modulating hormonal action can have a suite of beneficial and nonbeneficial effects. This is particularly seen for hormone replacement therapy and for agents capable of treating or preventing breast cancer through hormonal effects. Davis et al. presented a framework for viewing the impact of complex hormonal interactions on breast cancer risks through the lens of the precautionary principle while pointing out that certain phytoestrogens appear to be protective [18]. And a recent *New York Times* editorial argues for the continued use of DDT for the prevention of malaria despite the acknowledged harmful effects of DDT [19].

It is unclear whether the current interest in the precautionary principle reflects a move toward heightened concern about health and safety in developed countries in keeping with increased longevity and a feeling of health entitlement. An alternate explanation may be a world view that prefers natural

over synthetic products, that is willing to accept phytoestrogens with little or no concern, but wishes no possible exposure to "unnatural" sources of hormonal agents. The latter view is supported, at least in the United States, by the fact that in the case of herbal agents, many of which contain high levels of estrogenic substances to the point of toxicity [20], the burden of proof was actually shifted against precaution. The 1994 Dietary Supplement Act now requires the U.S. Food and Drug Administration prove harm before regulating these products.

One scientific approach that should come into increased use in a world in which the precautionary principle is a major regulatory approach is that of surveillance. Intervention before there are adverse effects can best be accomplished if there is sufficient investment in developing and measuring early indicators of exposure and effect, coupled with an understanding of human and ecosystem susceptibility. In the case of EASs, the decrease in most locales of body and ecosystem burdens of dioxins and PCBs is reassuring to the extent it suggests that the worst has been seen, but the seeming increase in burdens of polybrominated agents raises reasons for concern in keeping with an argument for precautionary action.

PERSISTANT ORGANIC POLLUTANTS

There are a number of facets of the EAS issue as it relates to persistent organic pollutants (POPs) that appear to be particularly pertinent to the precautionary principle. Notable about many of the agents that are under this heading is that their toxicity to humans remains less than fully convincing. The Seveso accident led to sufficient dioxin exposure to cause full-blown cases of chloracne, a skin condition that is diagnostic of significant body burdens of dioxins and related compounds. Yet there have been no clearly demonstrable long-term effects in the more than two decades of follow-up. One controversial finding has been a difference in birth ratio consistent with an EAS effect, but this is still unconfirmed and the issue of the effect of persistant organic pollutants (POPs) on sperm counts and birth ratios remains controversial [21,22]. While in some cases POPs are unquestionably animal carcinogens, and are capable of causing endocrine effects at high doses in laboratory tests, the evidence for adverse effects in humans remains controversial. For others, such as PCBs, the effects in humans at high doses are unquestionable and, at least in part, are expressed through endocrine disruption [1,23].

To some advocates of the precautionary principle, debates as to the human health effects of POPs are almost meaningless. The key issue is that these compounds are both persistent in the environment and harmful to ecosystems. Under the precautionary principle, such compounds should be banned without any further debate as to their effect in humans.

On the other hand, those arguing against the need for the precautionary principle as an additional regulatory approach can also use the history of the control of POPs. Traditional POPs such as PCBs are banned and no longer acceptable for use in OECD (Organization for Economic Cooperation and Development) countries. Most importantly, research has led to predictive approaches and assays that permit recognition of persistence as a characteristic of a new chemical before it is marketed. The availability of these predictive approaches, coupled with the significant legal and financial penalties that are now imposed on a chemical company that markets a persistent organic compound, make it highly unlikely that any reputable chemical company will move forward on developing or marketing such a compound.

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