International Journal of Occupational Medicine and Environmental Health, 2004; 17(1): 91—102

COMMENTARY: THE ROLE OF TOXICOLOGY IN PREVENTION AND PRECAUTION

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Abstract. Advocates of the Precautionary Principle have recently called for a "new science" to support the goals of precaution-based environmental and occupational health policy. While much attention has been given to epidemiology, the evidentiary science most relevant to precaution, or prevention, is toxicology. Opportunities for enhancing the role of toxicology in public policy must consider current biases in the field. Thus, rather than a "new science", advocates for change should focus upon ensuring that current scientific methods are appropriate and that interpretations of scientific data are accurate.

Key words:
Precaution, Prevention, Toxicology, Risk assessment

INTRODUCTION

The Precautionary Principle, originally expressed in several international treaties and in the Rio Declaration in 1992 [1], has been proposed with increasing vigor as an alternative framework for environmental policy, largely in response to failures and slow progress of current risk assessment based policy-making processes. The operational definition of this principle remains unclear, and its real implications for national and international policies are not fully explicated. To date, the "precautionary approach" has most often been cited in support of increasing the pace and scope of controls on relatively well characterized toxic chemicals (such as the persistent organic pollutants, which are largely the "old" organochlorine insecticides, phthalates used in plastics, and polychlorinated biphenyls and structurally similar byproducts of industrial processes, incinerators, and paper bleaching) [2]. The application of precaution with respect to these issues hardly requires any new science at this point, although retrospective analyses have argued that credible evidence of their hazards should have prompted earlier actions than those taken in the 1970s by many countries [3].

The United States is frequently cited as the major obstacle to the application of the Precautionary Principle in environmental and occupational health [2,4,5]. With the repeal of much of the Delaney Clause (of the Food, Drug and Cosmetic Act) by passage of the Food Quality Protection Act, all relevant US statutes now require formal risk assessments for supporting regulatory decisions. Nonetheless, as acknowledged by Wahlstrom [6], who claims that precaution has been a formal element of environmental policy making in Sweden since 1972, the US in many cases took major actions prior to Sweden, as in the case of legally binding decisions to ban polychlorinated biphenyls (PCBs) or to remove lead from gasoline.

The author was supported in part by grants from the Heinz Family Foundation and the Center for a Livable Future, Johns Hopkins.
Received: January 19, 2004. Accepted: January 30, 2004.
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SCIENCE AND PRECAUTION

This commentary responds to recent proposals by some advocates of the Precautionary Principle and other critics of current occupational and environmental health policy for a "new science" to support the goals of precaution. Impatience with science and scientists in environmental policy has a long history. Senator Edmund Muskie, in hearings in the US Senate on the first Clean Air Act in 1971, famously responded to the on-the-one-hand, on-the-other-hand testimony by several scientists with the comment: "Give me some one-handed scientists!"

What "new science" actually means is not entirely clear, but some indicators may be found in Table 1, comparing "mechanistic science" with "precautionary science" [7]. While many scientists would take issue with the asserted characteristics of "mechanistic science", it is important to note that these descriptions are perceived as true by many advocates of change in environmental policy (for example, as eloquently argued by O'Brien [5].

More recently, Kriebel et al. [8] published a consensus statement concerning the "science of precaution", based upon a meeting held at the University of Massachusetts-Lowell:

"Environmental scientists play a key role in society's response to environmental problems, and many of the studies they perform are intended ultimately to affect policy… [We] examine the implications of the precautionary principle for environmental scientists, whose work often involves studying highly complex, poorly understood systems, while at the same time facing conflicting pressures from those who seek to balance economic growth and environmental protection. In this complicated and contested terrain, it is useful to examine the methodologies of science and to consider ways that, without compromising integrity and objectivity, research can be more or less helpful to those who would act with precaution. We argue that a shift to more precautionary policies creates opportunities and challenges for scientists to think differently about the ways they conduct studies and communicate results".

Over the past two decades in the US, the practice of allegedly science-based environmental policy making has been smirched by misuses of scientific data, biases in scientific reviews, and the frequent invocation of "more research" as a means of delaying decisions to take action (the failure to decide can constitute an action of substantial impact, as described by the European Environment Agency (EEA) [3] and O'Brien [5]. Very recently, claims were raised in

Table 1. Characteristics of mechanistic and precautionary science [7]

	Mechanistic science	Precautionary science
Authority of Science/Scientistis	■ Separation of science from social issues ■ Exclusive peer review system ■ Closure and consensus	■ Multidisciplinary approaches ■ Inclusive peer review ■ Co-problem solving ■ Open-ended dialogue
Definitions of harm	■ Direct harm measured by few variables	■ Disruption of biological, ecological, or social systems ■ Ecological or evolutionary time and multigenerational
Points of reference	■ Molecular or organisms time ■ Human	■ Nature ■ All species
Error and burden of proof	■ Type I minimized ■ Type II maximized (fewer false positives) ■ Burden on public ■ Explanation in terms of causality	■ Type II minimized (fewer false negatives) ■ Burden on proponents/producers ■ Explanations in terms of pattern and association
Evidence and data	■ Empirical, experimental ■ Quantitative ■ Replicable ■ Deductive	■ Analytical, experiential, empirical and experimental ■ Qualitative and quantitative ■ Inductive and deductive
Uncertainty	■ Lack of data or extrascientific	■ Indeterminancy

the UK of interference by government scientists with the research by Prof. Andrew Stirling, an academic critic of biotechnology. But the question is whether a "new science" is needed, or whether current methods and practice in the environmental sciences need more protection and independence. In this paper I will argue that proponents of precaution should demand better, rather than different, science. Moreover, I argue that the delays between early warnings and late actions are due much more to politics and interest groups, rather than to inherent flaws or systematic errors in science, as implied by Barrett and Raffensperger [7] and Kriebel et al. [8].

There is also the danger that by calling for "new science", advocates run the danger of ceding the defence of current scientific research to their adversaries. Much of the unfinished business in international environmental and occupational policy could be resolved by acting upon the findings of current science – for example, there is ample evidence on anthropogenic impacts on global climate, antibiotic resistance associated with agricultural use of antibiotics for growth promotion, carcinogenicity of all asbestos compounds, adverse impacts of endocrine-active pesticides on wildlife. There is no need to argue from uncertainty for precaution in these and many other cases. We should also note that reforming the role of science and scientists in environmental policy making has received scrutiny from other stakeholders with a very different agenda from the Precautionary Principle. The recent Data Quality Act [9], enacted rather secretively in the US in 2000 as 27 lines in a giant budget bill, requires regulatory agencies to establish procedures "ensuring and maximizing the quality, objectivity, utility and integrity" of scientific information and statistics utilized by federal agencies. This requirement will impose burdensome rules on government and real disincentives on scientists whose work may be selected in the process of regulation or standards setting by government. In the guise of "better science", the government will now be required to make available the sources and data utilized in those studies by the agency or any third party (such as an environmental Non-Govermental Organization – NGO) or a labour union that are deemed influential in rulemaking. While this requirement will be onerous on government, it may well be terrifying to scientists outside government, mindful of the recent experiences of Herbert Needleman and Joel Schwartz, both outstanding scientists, who were harassed by industry over their highly important and influential research on lead poisoning and particulate air pollution [10].

THE ROLE OF TOXICOLOGY IN PREVENTING OCCUPATIONAL AND ENVIRONMENTAL DISEASE

This paper discusses the role of toxicology in implementing a precautionary approach because its importance and relevance has been underappreciated, while debates have focussed on the continuing uncertainties of epidemiological evidence. For instance, MTBE is the only example in "Late Lessons from Early Warnings" [3] in which the "early warning" involves toxicology to a significant extent. Among the evidentiary sciences that are relevant to public health, toxicology can make unique contributions to supporting prevention policies. In comparison, epidemiology at best can identify or evaluate environmental risk factors as causes of health and disease only after the fact of exposure and detectable health effects in exposed people. Even the most astute case studies, such as Thelwell Jones' reports on systemic disease among workers at ICI exposed to PCBs in the 1930s [11], and even John Snow's inferential intervention to remove the Broad Street pump handle [12], often cited as the first example of precaution [3], took place after significant exposures and obvious effects had occurred. Toxicology, specifically experimental toxicology, is the only opportunity we have to obtain information on hazards and risks before significant or widespread exposure of humans and other valued species. For that reason, most industrial countries require toxicological evaluations of drugs, pesticides, and other chemicals prior to their manufacture or marketing [13]. For agents such as drugs, clinical testing of safety and efficacy must be preceded by extensive testing in animals.

This paper focuses on toxicology, therefore, because of its importance in advancing preventive policies. I deliberately chose the term "prevention". Prevention has a long and meaningful history in medicine, public health, and health

policy, and by claiming a common purpose and continuity with the history of public health, the advocates of the Precautionary Principle may defuse some of the controversy engendered by the word "precaution" and an overemphasis on the need to act in the absence of evidence. The obligation to use precaution and foresight are well described in many of the controversial issues in 20th century epidemiology, including the history of understanding smoking and cancer. As stated by Stolley and Lasky [12] in their history of epidemiology: "After 1964, epidemiologists became increasingly occupied with describing the health effects of smoking. While the tobacco industry and policy makers continued to debate the implications of scientific findings, farsighted epidemiologists turned their attention to disease prevention and health promotion" [12]. In this same context of arguments over occupational and environmental risks, Bradford Hill in 1965 proposed concepts for assessing causality in non-experimental epidemiology. Hill's criteria are widely cited in misapplication as "gatekeepers" for admitting evidence to legal or government decision making; however, less frequently cited is his eloquent statement on the ethical imperative for preventive action in the absence of conclusive evidence of causality. Bradford Hill included biological plausibility as an important element in inferring causality [14]. It is rare that evidence relevant to mechanism or biological plausibility can be adduced from studies of humans without the opportunities provided by experimental research, such as toxicology, to examine the biological events linking exposure with disease.

The importance of toxicology is clearly demonstrated by the weight given by the International Agency for Research on Cancer (IARC) and the National Toxicology Program of the US (NTP), among other authorities, to rodent bioassays to determine carcinogenic properties of chemical and other exposures. Toxicology data alone can support the decision to list a chemical as a likely or probable human carcinogen [3,15]. Most dramatically, toxicological data were utilized by IARC in upgrading 2,3,7,8-tetrachlorodibenzo-p-dioxin to a Group I human carcinogen, based upon the demonstration of molecular mechanism of action and its cross species conservation [16]. Not surprisingly, the power of toxicology to identify potential carcinogenic hazards has elicited a substantial backlash, as exemplified by Ames and Gold [17].

In risk assessment based policy making, toxicology often plays the dispositive role. First, toxicity testing program are the major source of new information on hazard, that is, the potential of a chemical to cause adverse health effects. Second, toxicological studies are often the preferred source of precise information on dose and response because experimental design can control most of the confounders and uncertainties related to exposure assessment in observational epidemiology. Toxicology provides information on dose, including initiation and duration of exposure, route of exposure, and complete data on internal dose. In observational epidemiology, exposure must often be inferred from less direct measures such as job category or employment duration (for occupational studies), or ecologic indicators such as residence, market basket surveys, or ambient air or water quality (for environmental epidemiology). While the use of biomarkers (such as blood lead and lymphocyte DNA adducts) can move exposure assessment inside individuals, the interpretation of these data depends upon knowledge of toxicokinetics – including uptake, distribution, metabolism, and half-life – almost always obtained from toxicology. The relationship between internal dosimeters such as biomarkers and internal dose at the site of toxic action can never be measured in human subjects. Most of the currently utilized biomarkers of exposure, susceptibility, and response were first identified and validated in animal models or cell systems.

Toxicology can also refine dose:response by allowing us to redefine response at the preclinical level, through the examination of physiological, cellular, and molecular events biologically relevant to and precedent to the health endpoint of concern. While epidemiology may "count the dead bodies," as is often said, toxicology can count the alterations in gene expression. One of the most powerful examples of toxicological redefinition of response can be found in the risk assessments for 2,3,7,8-TCDD, in which molecular events of altered signal transduction and gene expression in liver, rather than tumorigenesis, was defined

as the response biomarker for cancer; this conceptual change justifies very low standards to guide regulation and risk reduction [18].

Precision of dosimetry and sensitivity of response definition are essential for development of dose:response metrics, the second step in risk assessment. Without this, it is not possible to use risk assessment as a preventive methodology since it is the dose:response curves generated by toxicology, rather than epidemiology, that have permitted extrapolation to levels of exposure that meet public health goals of prevention, even though these are orders of magnitude below those that can actually be tested or observed [11]. Risk assessment is sometimes criticized for its lack of testability with epidemiological studies. This criticism ignores the use of risk assessment as an instrument of prevention, to justify health policies and interventions designed to prevent adverse events, such as cancers or birth defects, at the very low rates that are goals of public policy – 10^{-4} to 10^{-6} – that could never be observed in epidemiology.

THE FAILURE OF TOXICOLOGY IN PREVENTION

Despite its promise, toxicology has not always supported preventive policies in occupational and environmental health. The recent record shows that toxicological findings have too often been applied to hinder prevention. Too often toxicological data are used to contradict epidemiological results (somewhat more rarely, vice versa), to delay decision making, or to contradict or obscure other research data. Finally, industry has until recently dominated the field of toxicology, as evidenced by the longtime acceptance by the Society of Toxicology of major financial support from the tobacco industry. These issues are discussed below. In a perverse involution of its role in supporting inferences of causality in epidemiological observations, toxicology has been recently used to contradict both epidemiology and toxicology, primarily through the partial citation of mechanistic data to counter organismic data on the same topic. Some notable examples of using toxicology to contradict epidemiology are shown in Table 2.

Table 2. Apparent contradictions of epidemiology with toxicological data

Cigarette smoke	No animal model of cigarette smoke-induced lung cancer [19]
Benzene	Rodents fail to get human leukemias and dosimetry in animals does not support low dose risk assessments for humans [20,21]
Arsenic	No evidence of genetic mutations in animals; hence risks cannot be assessed using standard models [22,23]

Note: references are to the proponents of these "contradictions".

Even the findings of the robust rodent bioassay have been challenged on the basis of mechanism in the case of several agents, such as: formaldehyde (post-cytotoxic regenerative hyperplasia), several thyroid carcinogens (gross imbalance in thyroid endocrinology), renal carcinogens (induction of a male rodent-specific low molecular weight protein), and stomach and bladder carcinogens (local irritation by insoluble deposits or calcifications), discussed in a recent IARC report [24]. This antitoxicological toxicology has been utilized to downgrade several chemicals with important occupational exposures, including the pesticide amitrole and the industrial chemical ethylenethiourea, two thyroid carcinogens recently downgraded to Group 3 (not classifiable as to its carcinogenicity to humans) by IARC. It should be noted, nonetheless, that mechanistic data have also been influential in upgrading the evaluation of toxic chemicals, including carcinogens [15]. In these misuses of toxicology, we may echo Galileo: "*Eppur si muove*" – yet they are still carcinogens. At best, the search for mechanism can introduce extraordinary delay. Lack of mechanistic insight is not a justification for delay, especially in cases where the observational data from epidemiology or toxicology are strong. The dioxin risk assessment process in the US is an egregious example of how "more research" has been used to excuse nearly 20 years of failure to set final guidelines. In contrast, the history of lead regulation more closely exemplifies appropriate interactions between research and decision making (Table 3). The early reports of subencephalopathic lead toxicity in young children, coupled with local data on lead exposures and air lead levels, were sufficient to prompt

the Environmental Protection Agency (EPA) in 1976 to propose limits on lead in leaded gasoline [25].

In 1979, the first major study by Needleman et al. [31] and his colleagues prompted a re-evaluation of public health policy. Together with further data on lead exposures and the risk of gasoline lead, the EPA overruled an express decision by the Reagan White House and began the total phase-out of lead in gasoline. Further studies in the 1980s supported the legislative decision in 1990 to end all leaded gasoline in the US. In retrospect, 15 years may seem too long for true prevention, but few if any regulatory decisions of similar magnitude have been made so rapidly or completely.

Toxicology's self-doubts may be seen in frequent misinterpretation of the Paracelsian aphorism "the dose makes the poison." As noted by Aldridge [36], Paracelsus meant his comments to be taken at a more sophisticated level than is done by some toxicologists. "The dose makes the poison" is a reasonable statement of dose and response; an unreasonable corollary some have drawn is that for every toxic agent there is a nontoxic dose. Alternatively, neo-Paracelsans claim that everything at some dose is toxic, citing the fact that too much water, table salt, or potatoes [37,38] can kill you.

The financial situation of toxicology is of great concern, apart from the involvement of industry toxicologists in regulatory decision-making without sufficient counterweight from the public health and public interest community. The vast majority of toxicity testing has always been conducted by industry either in house or through contract laboratories. Concerns over the probity of this practice first arose at the US Food and Drug Administration (FDA), but it was the flagrant abuses in PCB studies conducted for Monsanto by Industrial Bio-test in the 1970s that resulted in the promulgation of Good Laboratory Practice (GLP) regulations. These rules, now adopted by all OECD countries, require extensive training, record keeping, and access to lab notebooks. Audits indicate that the general level of practice has improved, although problematic instances – particularly for pre-clinical and clinical drug testing – still occur.

At the same time, some of the best toxicological research in the US has been conducted by scientists at industries where toxicology laboratories have maintained a tradition of hiring excellent scientists, collaborating with academic researchers, and publishing study results in the peer-reviewed literature. Unfortunately most other companies

Table 3. Interplay of science and policy in removing lead from gasoline: US experience

1968	John Goldsmith [26] proposes a quantitative contribution of airborne lead to blood lead levels in human populations
1972	Under the Clean Air Act, unleaded gasoline introduced in US to prevent degradation of the catalytic converter, an antismog technology
1972	Studies by de la Burde and Choate [27] on subencephalopathic lead poisoning in children
1972	Needleman et al. [28] report on increased tooth lead concentrations in urban children
1974	Silbergeld and Goldberg [29] report lead causes hyperactivity in mice
1976	EPA proposes first reductions in lead content of leaded gasoline
1977	EPA sued by Ethyl, lead industries
1977	National Academy of Sciences publishes first air quality criteria document report on airborne lead; committee dominated by lead industry
1978	EPA upheld in court; phase down of lead in gasoline begins
1978	Silbergeld and Adler [30] propose no threshold for lead as a neurotoxin
1979	Needleman et al. [31] publishes first study on lead and neurobehavioral performance in children
1980	Patterson [32] documents major increases in environmental lead concentrations due to anthropogenic activities
1980	Second NAS report on lead is published with dissent by Patterson
1983	First report on longitudinal cohort study [33]
1983	Second phase down of lead in gasoline is unsuccessfully blocked by industry and White House
1985	CDC lowers guidance acceptable level of lead in children to 25 μg/dL
1991	Continued study on longitudinal cohort shows persistent deficits in children's behavior and school attainment among children exposed as infants [34]
1990	Clean Air Act amendments impose full phase out of lead from gasoline in the US
1991	CDC lowers guidance to prevent childhood lead poisoning to 10 μg/dL
1992	Long-term follow-up study shows persistent deficits due to lead [35]
1995	End of tetraethyl lead in automobile fuels in the US

have not maintained internal strength in toxicology. With the contraction of the drug and chemical industry over the past 10 years (by merger and by financial downturn), private sector investment in toxicology has greatly decreased. Apolicy of integrating research culture into applied toxicology cannot ensure rigour or integrity, but isolation can certainly impede these qualities.

Independent funding and support for toxicology came through the growth of the National Institute of Environmental Health Sciences (NIEHS). Starting with David Rall and continuing with Kenneth Olden, NIEHS has fostered toxicology through three critical mechanisms: responsibility for the NTP, the largest nonindustry testing program in the world, intramural research that provides scientific leadership to the field, and support for university-based research and training. As one of the first NIEHS-funded postdoctoral fellows in toxicology, and a recipient of NIEHS grants, I know the influence of the NIEHS on toxicology. Recently, NIEHS has contributed to international research and training in environmental health through the US National Institutes of Health (NIH) Fogarty Center.

The establishment of the Chemical Industry Institute of Toxicology (CIIT) in 1976 – under Robert Neal – was an interesting counterpoint to this major change in the balance of funding for toxicology. CIIT has carried out both client-based studies and more basic research in toxicology. CIIT's largest research program is funded by 31 member companies and the American Chemistry Council's Long-Range Research Initiative. Other financial support comes from government agencies (EPA and the NIEHS), independent organizations, trade associations, and corporations [39]. Since Neal, this research has had highs and lows. At times CIIT research has contributed to the delays in preventive health policy by raising mechanism-based objections to bioassay findings [40] or raising factors to explain away carcinogenicity data [41]. At other times, CIIT research has been important in supporting preventive policies, for example research on the toxicokinetics of inhaled manganese, originally sponsored by the Ethyl Corporation, manufacturer of a controversial organomanganese gasoline additive.

Recently, experiments in joint funding of toxicological research have been proposed, in which the US chemical industry has contributed to research initiatives managed by NIEHS. Views on this venture are considerably divided, but the process of review and the performance of funded scientists will follow the practice and requirements of NIH.

IMPROVING TOXICOLOGY – PACE AND PRODUCT

The most compelling critique of risk assessment as a tool of policy making is the long delay between hazard identification and intervention to reduce or prevent exposures [5,42]. However, toxicology is not the main reason for or source of delay. Most of the blame must be placed on the politics of environmental and occupational health. In fact, it is a major failure of the proponents of the Precautionary Principle to remain largely silent on the economic and political factors that delay timely action by private and public institutions. Unless these factors are recognized and examined, they will not be dispelled by even the most compelling rhetoric or most thoroughgoing changes in science.

Nonetheless, the increasing complexity of risk assessment, including requirements to detect new types of hazards (such as endocrine disruption), indisputably introduces delays and increases costs. The cost and complexity of toxicology testing has been one of the disincentives to requiring data on new and existing chemicals, at least in the US [13,43]. These factors have also provided a rationale for keeping the burden of proof as it is – that chemicals are safe until demonstrated otherwise (this assumption does not apply to pesticides in environmental policy).

Reducing the burden of demonstrating safety (or more accurately, excluding the likelihood of significant risk) has required significant changes in toxicology testing strategies. These changes may be only the beginning of a true and necessary transformation of toxicology and science-based policy.

THE ROLE OF THE NEW TOXICOLOGY AND PREVENTION

The first real strategic opportunity to introduce new approaches in toxicology has been introduced in the context

of the international High Production Volume (HPV) chemicals program. Developed first by a consensus decision of the OECD Environment Program, this undertaking is a voluntary commitment by the chemical industry to provide a minimum set of data to support initial hazard or safety assessments [44]. The HPV programme in the US came about after the NGO Environmental Defense analyzed a set of industrial chemicals made in amounts >1 million pounds/yr for data availability, and reported that most chemicals lacked minimal data on ecological or health risks [45].

The conceptual breakthrough in this analysis came from the utilization of a simple set of rapid and efficient tests, adopted by the OECD countries, as a "yardstick" for evaluating available information. This breakthrough eliminated the stalemate identified in an earlier assessment of chemical ignorance, in which it was not possible to define an adequate set of information [46]. Following upon the NGO analysis, similar analyses were conducted by the US chemical industry and the EPA. When their findings confirmed and extended the Environmental Defense' work, the voluntary chemicals "right to know" initiative was adopted in the US. It is designed to produce data sufficient for an initial safety assessment by 2006 on approximately 3000 chemicals. Producers bear the primary responsibility to generate this information, through one of several methods: release of hitherto proprietary data, completion of new testing, or the adoption of novel strategies. In some countries this testing is being undertaken by governments (e.g., the Netherlands), industry (US), or government-industry partnerships (Japan).

This goal is daunting, in terms of scientific and fiscal demands, as well as an increased burden of testing on animals. Added to the HPV program, there are now international and national initiatives to test most existing chemicals (the European Union chemicals policy) or to test for specific endpoints (such as the international endocrine disruptor testing program in the OECD, the children's health initiative in the US, the persistent/bioaccumulative/toxic chemical identification program in the Nordic countries, the new emphasis on ecotoxicology endpoints in Japan). To accomplish these goals, and to meet concerns of the animal welfare community, there is a real need to identify, validate, and use novel strategies for chemical testing, including alternative methods and improved structure-activity analyses to group chemicals into categories, whereby data are only required on some chemicals within a rationally defined group. The pace of completion remains a concern: as of October 2001, US industry had submitted commitments to provide information on 383 chemicals, of which over 90% were grouped in 28 categories and tests were proposed for only 27 individual substances (data from US EPA). Yet the validity of these categories is largely unproven.

Increased interest in real alternatives – tests that do not utilize whole animals – has also been stimulated by the EU chemicals policy and European legislation on cosmetics testing.

These challenges will require further changes in toxicology to meet the public's expectation for both information and humane science. Two of these are briefly discussed here.

TOXICO 'OMICS

As discussed by Olden [47], toxicogenomics (and proteomics and metabonomics, to include all the new high through put and molecular methods) holds several promises for supporting an increased role for toxicology in chemical safety evaluation with a "precautionary" perspective [47,48]. In this discussion I do not consider the separate potential uses of 'omics in standard setting, an issue that raises profound ethical concerns for many reasons. First, these technologies can provide rapid information on biological activity in terms of alterations in gene expression and protein synthesis, although interpretation of these molecular signals in most cases awaits much more contextual information than is available at present. Second, patterns of molecular responses can be used to support or reject such innovations as the proposed categories or groups of chemicals being encouraged in the HPV program. Third, selected molecular signals can be interpreted as indicators of the need for greater precaution based upon subgroup susceptibility (such as increased expression of CYP 450 genes known to be polymorphic,

or involvement of the estrogen receptor in cellular responses). Eventually, with the development of a large database, it may be possible to utilize these methods as a means or selection for further complex and time-intensive and animal-based testing.

ALTERNATIVES

The development of alternative methods (defined as methods that are less burdensome on live animals through refinement and reduction, as well as the substitution of entirely *in vitro* methods using cell systems or *in silico* computational approaches) is also being spurred by increased demands for information. Until this point, a major impetus for developing alternatives has been from the ethical perspective of animal welfare, sometimes embodied in legislation, as in recent German constitutional amendments. Up to this point, progress towards the development and validation of alternative methods has been slow. However, as pointed out by Goldberg and Frazier [49], attention to the "3Rs" (refinement, reduction and replacement) can in fact be an incentive to better science. Green et al. [50] have explicitly pointed out the opportunities and advantages of incorporating this perspective into meeting the demands of new testing initiatives. The new EU chemicals policy proposes an explicit encouragement of this by permitting or possibly requiring the use of alternatives for low to medium volume chemical testing. The combination of new legal requirements for information on chemicals, and the increasing burden of public demand for science-based decisions on chemical safety is likely to stimulate much greater support for alternatives and much more rapid validation of these methods [51]. This is likely to be best accomplished by the incorporation of insights from mechanistic toxicology and basic science into the goals of applied toxicology and regulation [52].

CONCLUSIONS

Calls for a "new" Precautionary Science spring from understandable impatience with the past century's record of delays and missed opportunities in environmental and occupational health policy. Dissatisfaction with current practice is expressed by many stakeholders in policy debates. Industry interests have often invoked "good science" to defend the *status quo*, demanding reforms in regulatory science. It is the thesis of this paper that an attack on science by either side is not justified. Analyses of missed opportunities for preventive interventions have largely cited examples where traditional scientific methods were more than sufficient to provide "early warnings" which were ignored for political reasons. Science (specifically toxicology) is not the root cause of delay and inefficiency in policy making. Improving science – or getting the information desired [8] – is best accomplished by pointing out omissions and misuses of current science, rather than calling for a new discipline. True prevention will be accomplished by demanding more science, rather than by calling for actions in the absence of science. The major demands stated by proponents of the Precautionary Principle concern chemicals that have been well characterized by scientific research [2–4]. For these risks, calling for "action in the face of uncertainty" is irrelevant. Identifying new risks, evaluating alternatives before making new mistakes (as called for by O'Brien [5] and as has happened in the substitution of halogenated diphenyl ethers for halogenated biphenyls as flame retardants), understanding the range and sources of human and ecosystems exposures – these efforts require more science in order to empower "foresight", where true prevention can be accomplished.

A FINAL NOTE OF PRECAUTION: WORDS, NOT DEEDS?

Much is made of the potential policy collision between the United States and the European Union over the legal exposition of the Precautionary Principle by the EU and its lack of standing in regulation and law in the US [3,4,13]. While the Principle is referenced by many instruments in the EU, an examination of actual policy making suggests that the Principle may be honored more in words rather than in deeds. As noted by the EEA review, many cogent examples of precautionary actions can be found in US policy making in the 20th century; it is the US that took

the first steps to reduce and ban many of the POPs, lead in gasoline, asbestos, PCBs, and several brominated flame retardants. The most egregious example of principled hypocrisy, however, concerns perfluorinated octanyl sulfates (PFOS), a family of structurally-similar chemicals used in many consumer products and manufactured in high volumes by many European Union countries, as well as Switzerland, Canada, Australia, and Japan. Concerns over PFOS arose with reports, by industry, that contrary to assumptions made on the basis of structure-activity relationships, PFOS did not seem to degrade [53], and that measurable levels of PFOS could be detected in blood samples from many populations, not exclusively workers exposed occupationally [54].

Over the past two years these findings were translated to the OECD by 3M and the US delegation, stimulating a remarkably rapid response of evaluation, monitoring, and testing by several companies and governments. PFOS possesses a broad spectrum of toxic activity, including effects on reproduction, target organ function, and it increases tumors in experimental animals. Also, very recent data provided to the OECD indicates that there is evidence for increased cancer risks among workers exposed to PFOS. Thus it would seem that there is sufficient "warning" to take actions to protect the health of workers and consumers. However, of all the OECD countries engaged in this issue, only the US has actually banned the production of PFOS, and only an American producer has agreed to this ban without protest. Talk is apparently easier than action.

ACKNOWLEDGEMENTS

This paper has benefited from continuing discussions with colleagues, especially Karen Florini of Environmental Defense; Profs Lynn Goldman and Thomas Burke of Johns Hopkins, as well as the opportunity to review the writings of Mary O'Brien and Carolyn Raffensperger. These colleagues will not agree with all of the conclusions in this essay, and I take sole responsibility for these statements. This paper is dedicated to Dr. Kenneth Olden for his leadership in ensuring the involvement of toxicology in important science policy issues.

REFERENCES

1. United Nations Conference on Environment and Development. *Rio Declaration on Environmental and Development. Rio de Janeiro, 1992* [cited 2003 Jun 27]. Available from: http://www.upnep.org/Documents/Default.asp? Document ID = 78 & Article ID = 1163.
2. McGinn AP. *Why poison ourselves? A precautionary approach to synthetic chemicals*. World Watch Paper 153, November 2000.
3. European Environment Agency. *Late lessons from early warnings: the precautionary principle 1896–2000*. Environmental Issue Report No. 22. Copenhagen: European Environment Agency; 2001.
4. Raffensperger C, Tickner J. *Protecting Public Health and the Environment: Implementing the Precautionary Principle.* Washington, DC: Island Press; 1999.
5. O'Brien M. *Making Better Environmental Decisions*. Cambridge: MIT Press; 1999.
6. Wahlstrom B. *The precautionary approach to chemicals management: a Swedish perspective*. In: Raffensperger C, Tickner J, editors. *Protecting Public Health and the Environment: Implementing the Precautionary Principle.* Washington, DC: Island Press; 1999. p. 51–69.
7. Barrett K, Raffensperger C. *Precautionary science.* In: Raffensperger C, Tickner J, editors. *Protecting Public Health and the Environment: Implementing the Precautionary Principle.* Washington, DC: Island Press; 1999. p. 106–22.
8. Kriebel D, Tickner J, Epstein P, Lemons J, Levins R, Loechler EL, et al. *The precautionary principle in environmental science.* Environ Health Perspect 2001; 109 9): 871–6.
9. Data Quality Act. Public Law 2000, 106–554.
10. Silbergeld EK. *Protection of the public interest, allegations of scientific misconduct, and the Needleman case.* Am J Public Health 1995; 85 (2): 165–6.
11. Silbergeld EK. *Understanding risk: The case of dioxin.* Sci Am Sci Med 1995; Nov/Dec: 48–57.
12. Stolley PD, Lasky T. *Investigating Disease Patterns. The Science of Epidemiology.* New York: WH Freeman and Company; 1995.
13. Davies JC, Mazurek J. *Pollution Control in the United States. Evaluating the System*. Washington, DC: Resources for the Future; 1998.
14. Silbergeld EK. *The role of toxicology in causation: A scientific perspective.* Courts Health Science Law 1991; 1: 374–85.

15. Huff J. *IARC Monographs, industry influence, and upgrading, downgrading, and under-grading chemicals: a personal point of view.* Int J Occup Environ Health 2002; 8(3): 249–70.

16. IARC Monogrphs on the Evaluation of Carcinogenic Risks to Humans. Vol. 69. *Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans.* Lyon: International Agency for Research on Cancer; 1997.

17. Ames BN, Gold LS. *Mitogenesis, mutagenesis, and animal cancer tests* [Review]. Prog Clin Biol Res 1991; 369:1–20.

18. Sewall CH, Lucier GW. *Receptor-mediated events and the evaluation of the Environmental Protection Agency (EPA) of dioxin risks.* Mutat Res 1995; 333(1–2): 111–22.

19. Coggins CRE. *A review of the chronic inhalation studies with mainstream cigarette smoke in rats and mice.* Toxicol Pathol 1998; 26: 307–14.

20. Cole CE, Tran HT, Schlosser PM. *Physiologically based pharmacokinetic modeling of benzene metabolism in mice through extrapolation from in vitro to in vivo.* J Toxicol Environ Health A 2001; 62 (6): 439-65.

21. Farris GM, Robinson SN, Gaido KW, Wong BA, Wong VA, Hahn WP, et al. *Benzene-induced hematotoxicity and bone marrow compensation in B6C3F1 mice*. Fundam Appl Toxicol 1997; 36(2): 119–29.

22. Gebel TW. *Unanswered questions in arsenic toxicology.* J Environ Pathol Toxicol Oncol 2001; 20(4): 299–309.

23. Wei M, Wanibuchi H, Morimura K, Iwai S, Yoshida K, Endo G, et al. *Carcinogenicity of dimethylarsinic acid in male F344 rats and genetic alterations in induced urinary bladder tumors.* Carcinogenesis 2002; 23(8): 1387–97.

24. Capen CC, Dybing E, Rice JM, et al., editors. *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis.* IARC Scientific Publications No. 147. Lyon: International Agency for Research on Cancer; 1999.

25. Silbergeld EK. *Preventing lead poisoning in children*. Ann Rev Public Health 1997; 18: 187–210.

26. Goldsmith JR, Hexter AC. *Lead intake from food and from the atmosphere.* Science 1968; 159(818): pp. 1000.

27. De la Burde B, Choate MS, Jr. *Does asymptomatic lead exposure in children have latent sequelae?* J Pediatr 1972; 81(6): 1088–91.

28. Needleman HL, Tuncay OC, Shapiro IM. *Lead levels in deciduous teeth of urban and suburban American children.* Nature 1972; 235(5333): 111–2.

29. Silbergeld EK, Goldberg AM. *Lead-induced behavioral dysfunction: an animal model of hyperactivity.* Exp Neurol 1974; 42(1): 146–57.

30. Silbergeld EK, Adler HS. *Subcellular mechanisms of lead neurotoxicity*. Brain Res 1978; 148(2): 451–67.

31. Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, et al. *Deficits in psychologic and classroom performance of children with elevated dentine lead levels.* N Engl J Med 1979; 300(13): 689–95.

32. Settle DM, Patterson CC. *Lead in albacore: guide to lead pollution in Americans.* Science 1980; 207(4436): 1167–76.

33. Bellinger DC, Needleman HL. *Lead and the relationship between maternal and child intelligence.* J Pediatr 1983; 102(4): 523–7.

34. Bellinger DC, Stiles KM, Needleman HL. *Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study.* Pediatrics 1992; 90(6): 855–61.

35. Bellinger D, Sloman J, Leviton A, Rabinowitz M, Needleman HL, Waternaux C. *Low-level lead exposure and children's cognitive function in the preschool years.* Pediatrics 1991; 87(2): 219–27.

36. Aldridge WN. *The biological basis and measurement of thresholds.* Ann Rev Pharmacol Toxicol 1986; 26: 39–58.

37. Charles GD, Linscombe VA, Tornsi B, Mattsson JL, Gollapudi BB. *An in vitro screening paradigm for extracts of whole foods for detection of potential toxicants*. Food Chem Toxicol 2002; 40(10): 1391–402.

38. Silbergeld EK. *The hazards of synthetic (anthropogenic) chemicals.* Toxicol Letters 1995; 82/83: 835–41.

39. About Chemical Industries Institute of Toxicology [cited Oct 2002]. Available from: http://www.ciit.org.

40. Swenberg JA, Lehman-McKeeman LD. *α2-Urinary globulin-associated nephropathy as a mechanism of renal tubule cell carcinogenesis in male rats.* In: Capen CC, Dybing E, Rice JM, et al., editors. *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis.* IARC Scientific Publication No. 147. Lyon: International Agency for Research on Cancer; 1999. 95–118.

41. Irons RD. *Studies on the mechanism of 1,3-butadiene-induced leukemogenesis: the potential role of endogenous murine leukemia virus.* Environ Health Perspect 1990; 86: 49–55.

42. Dorman DC, Brenneman KA, McElveen AM, Lynch SE, Roberts KC, Wong BA. *Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain*. J Toxicol Environ Health A 2002; 65(20): 1493–511.

43. Silbergeld EK. *Risk assessment: the perspective and experience of US environmentalists.* Environ Health Perspect 1993; 101(2): 100–4.

44. U.S. Environmental Protection Agency. *Chemical right-to-know initiative* [cited Oct 2002]. Available from: http://www.epa.gov/chemrtk.

45. Environmental Defense. *Toxic Ignorance: the continuing absence of basic health testing for top-selling chemicals in the United States.* Washington: Environmental Defense; 1997.

46. National Research Council (NRC). T*oxicity testing: strategies to determine needs and priorities.* Washington, DC: National Academy Press; 1984.

47. Olden K, Guthrie J, Newton S. *A bold new direction for environmental health research*. Am J Public Health 2001; 91(12): 1964–7.

48. Waring JF, Halbert DN. *The promise of toxicogenomics.* Curr Opin Mol Ther 2002; 4(3): 229–35.

49. Goldberg AM, Frazier JM. *Alternatives to animals in toxicity testing.* Sci Am 1989; 261(2): 24–30.

50. Green S, Goldberg AM, Zurlo J. *The TestSmart-HPV Program–development of an integrated approach for testing high production volume chemicals*. Regul Toxicol Pharmacol 2001; 33(2): 105–9.

51. Balls M, Goldberg AM, Fentem JH, Broadhead CL, Burch RL, Festing MF, et al. *The three Rs: the way forward: the report and recommendations of ECVAM Workshop 11*. Altern Lab Anim 1995; 23(6): 838–66.

52. Seiler A, Visan A, Pohl I, Genschow E, Buesen R, Spielmann H. *Improving the embryonic stem cell test (EST) by establishing molecular endpoints of tissue specific development using murine embryonic stem cells (D3 cells).* ALTEX 2002; 19 Suppl 1: 55–63.

53. Giesy JP, Kannan K. *Distribution of perfluorooctane sulfonate in wildlife*. Environ Sci Technol 2001; 35(7): 1339–42.

54. Olsen GW, Burris J, Mandel JH, Zobel LR. *Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees.* J Occup Environ Med 1999; 41(9): 799–806.