**INTRODUCTION**

The issue of what is the purpose of a risk assessment has been the topic of debate within a past BELLE Newsletter. This topic was selected since a document prepared by EPA in 2004 clearly stated that "as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned." It is clear that this "guiding" perspective needs to be the subject of much public discussion and debate, not simply the de facto statement by members of the EPA Risk Assessment Task Force. In Volume 13, Number 1, July 2005 of the BELLE Newsletter the logic of this "guiding" perspective was discussed and debated by a wide range of non-governmental scientists from within the United States. However, it was felt that this issue would benefit from an expanded range of perspectives, especially with an international favor. Therefore, this issue of the Newsletter has its lead article by Hanekamp and Bast from the Netherlands which critically assessed the EPA position and its broad national and international implications and well as scientific foundations. This lead paper was then subjected to critical expert commentaries, again with international perspectives from scientists in the UK, The Netherlands and the US. Finally, Hanekamp and Bast were invited to have the "final" word of the Newsletter, but a final word which we hope stimulates much further discussion.

Edward J. Calabrese

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**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION: Edward Calabrese</td>
<td>1</td>
</tr>
<tr>
<td>HORMESIS IN PRECAUTIONARY REGULATORY CULTURE: MODELS PREFERENCES AND THE ADVANCEMENT OF SCIENCE</td>
<td>2</td>
</tr>
<tr>
<td>Jaap C. Hanekamp and Aalt Bast</td>
<td></td>
</tr>
<tr>
<td>COMMENTARY: PRECAUTIONARY PRINCIPLE FOR TOXIC CHEMICALS - NO ALTERNATIVE TO SAFEGUARD SOCIETAL BENEFITS</td>
<td>19</td>
</tr>
<tr>
<td>Dr. Thomas Jostman</td>
<td></td>
</tr>
<tr>
<td>COMMENTARY: PRECAUTION, INSTITUTIONS, INCENTIVES, HEURISTICS, REGULATION AND HORMESIS</td>
<td>21</td>
</tr>
<tr>
<td>Julian Morris, Ph.D.</td>
<td></td>
</tr>
<tr>
<td>COMMENTARY ON HORMESIS AND PRECAUTION: THE TWAIN SHALL MEET</td>
<td>24</td>
</tr>
<tr>
<td>PF Ricci and TR MacDonald</td>
<td></td>
</tr>
<tr>
<td>RESPONSE TO COMMENTATORS</td>
<td>35</td>
</tr>
<tr>
<td>Jaap Hanekamp and Aalt Bast</td>
<td></td>
</tr>
<tr>
<td>2006 CONFERENCE PROGRAM</td>
<td>37</td>
</tr>
<tr>
<td>INTERNATIONAL HORMESIS SOCIETY</td>
<td>40</td>
</tr>
<tr>
<td>IHS APPLICATION FOR MEMBERSHIP</td>
<td>41</td>
</tr>
<tr>
<td>ADVISORY COMMITTEE</td>
<td>42</td>
</tr>
</tbody>
</table>
ABSTRACT
The article focuses on flaws in the actual approaches of exposure to a chemical of recipient organisms. It demonstrates the excessive use of arguments based on adverse effects and underlines the necessity to take adaptive effects seriously. Regulators are invited to rethink their inclination to the 'When in doubt, keep it out.' precautionary approach, with results in counter-productive and costly regulations. The authors are clear about the necessity to include hormesis, in the form of a TIE (toxicological insignificant exposure level) related to the concentration, as a regulatory translation of adaptive effects. This inclusion might well be the 'brake' for the looming 'collision' with reality of the actual linear toxicological models. This analysis includes the advice to EPA, not to follow the 'witch hunt of synthetic chemicals' as embodied in the EU REACH program.

INTRODUCTION
It is recognized that a diversity of opinion exists regarding what is 'adverse' versus 'adaptive,' both within EPA and in the general scientific community. At present, there is no Agency-wide guidance from which all health assessors can draw when making a judgment about adversity. Therefore, various experts may have differing opinions on what constitutes an adverse effect for some changes. Moreover, as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned.

As a further look at this issue, an 'adaptive' example is used. The human body is capable of adapting to certain toxic insults. When adaptive responses become adverse and irreversible is not yet defined. In cases where data are not available to determine when the capacities of repair mechanisms are exceeded and adaptive responses become toxic, health assessments are based on any adverse response that is deemed biologically significant. As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events.1

These statements of the EPA—in their examination of risk assessment principles and practices—show an unambiguous preference for a 'steady-state' approach of toxicology. By that we mean that the toxicological research into potential biological active compounds (e.g. carcinogens) should focus on a non-interference of the biological homeostasis by the scrutinised chemical compound of a specific (experimental) organism. The organism—in a manner of speaking—should remain as it was before the challenge with the compound under scrutiny. (Obviously this requires a whole range of dose-response challenges.)

What is interesting is that the EPA does recognise the existence of the so-called adaptive response (either in non-adverse or beneficial terms) but regards the existence as non-relevant for the actual assessments done by the EPA. The EPA thereby openly implements a bias in its risk assessment methodology. In this article we need to take a closer look at this bias both from a cultural and a scientific perspective, as it is clear that the introduced bias is a result of so-called precautionary culture, which has become a common denominator to describe contemporary Western culture.2 For that reason we will start our commentary on the EPA position with a concise portrayal of contemporary culture and the position of science therein.

Our contention is that hormesis as a scientific account of the relation between dose and response will successfully question the current linear toxicological paradigm in the scientific arena. However, as knowledge and power are much more interrelated in precautionary culture and as a result autonomous knowledge is increasingly questioned, criticism against hormesis—despite its growing scientific merit—will come from the public (political) arena that regards hormesis as a threat to regulatory strength in the field of chemicals regulation and the like. Before we delve into the issue we will first take a look at science itself.
A Framework of Science

The status of scientific knowledge in relation to environmental issues has become increasingly important and demands some scrutiny, as it impacts the perspective on precaution. How scientific knowledge is understood and actually used impinges on the ways in which environmental issues are viewed. We therefore need to first establish a framework in which the scientific endeavour can be positioned, and whether or not worldviews and ideologies shape and influence the process of scientific research.

Before we do that we need to distinguish between actual science and good science, and the way worldviews actually or in theory does (should) or does not (should not) impact the developing of theories and explanations, and the way experimentation is set up. The Lysenko affair is a prime historical example of the (in this case catastrophic) influence of worldviews on science. However, from this historical example (and there are many others to give) that actual science is not always good science, does not inevitably follow that good science should be wholly identical with actual science.

The refutation of the existence of worldview neutral science—as so often stated with reference to especially the work of Kuhn—does not result from one or even multiple examples. If good science should be worldview neutral—that is to say that it is not aligned to or does not support a particular ideology, religion or worldview over another—then the activity of science needs to be specified more precisely. Weber, for instance, asserts that results form scientific work is value-free if they do not contain any judgement of personal, cultural, moral or political value. In this particular sense, science is worldview-neutral. However, values cannot, Weber emphasises, be eliminated when it comes to what scientists choose to investigate. In this particular sense science is not worldview-neutral. Therefore, in order to refine the issues of (partial) worldview influences and elucidate the actual locations of these influences, it is helpful to distinguish four different stages of the scientific modus operandi, which we later on will apply to the debate of environmental and public health issues, the role of precaution, and the status of the hormesis within the discipline of toxicology.

1. The problem-stating phase of science (science₁)
2. The development phase of science (science₂)
3. The justification phase of science (science₃)
4. The application phase of science (science₄)

In relation to science₁, scientists must first decide what is worth studying, what they want to spend their time, energy and their own or other people’s money on. This might seem a trivial matter, yet Imre Lakatos expressed his trepidations on this matter already some decades ago quite clearly:

“In my view, science as such, has no social responsibility. In my view it is society that has a responsibility—that of maintaining the apolitical, detached scientific tradition and allowing science to search for truth in the way determined purely by its inner life. Of course, scientists, as citizens, have responsibility, like all other citizens, to see that science is applied to the right social and political ends. This is a different, independent question.…”

Lakatos’s concern was that science₁—the problem-stating phase of science—is threatened by political (ideological) interference. Obviously, in the contemporary scientific enterprise, this political influence has materialised more extensively than Lakatos might have anticipated. Research efforts usually require large sums of money, which results in the mandatory involvement of governments and economic parties who can actually supply the necessary funding. Consequently, people in power often decide the kind of research that ’should’ be initiated, and the kind that ’should be neglected. Science₂—in short—has become heavily politicised and commercialised. This could lead to a situation in which a particular ideology or worldview is allowed to shape too heavily the problem-stating phase of science, which—we believe—is the case with numerous environmental and public health research issues. (To be sure, scientific work has never been a detached enterprise, and doesn’t need to be.)

After scientists have chosen their research arena, and have defined their problems to be solved, they then try to devise methodologies suitable for solving these problems, and try to develop hypotheses that would provide adequate explanations of phenomena under scrutiny and test them against what they consider to be evidence. If evidence is lacking or insufficient to corroborate the hypotheses, scientists try to find better and more conclusive evidence. This—in Stenmark’s terminology—is the development phase of science, science₂. This phase of the scientific enterprise is not without its problems in relation to worldview influence. One particular issue has to do with the fact that if a certain group of people with a particular worldview dominates a certain scientific arena, then their political commitment could well hinder development of certain hypotheses that might better explain empirical data than actually are developed by this group of people.

The application phase of science—science₃—is the most obvious candidate for worldview influence. Indeed, the demarcation between traditional knowledge institutions such as universities and research institutions run or financed by governments, non-governmental organisations or industry has eroded. Scientific knowledge construction or theory formation is now generated to a major extent with a perspective specifically on application. Here, the societal (political) expectations of science’s ability to provide clear-cut useful answers to an escalating range of issues and problems surfaces most poignantly. What ‘useful’ means of course depends on the particular worldview one holds and one’s position towards government, industry, NGO, and the like.

Invented concepts and empirical data are discussed at conferences, published in peer reviewed scientific journals and the like (and might even make to the public media). In the justification phase of science—science₄—scientists try to convince the rest of the scientific community of the adequacy of the explanations they have put forward on the different (scientific) platforms of communication in order to have their theories accepted as a part of the corpus of scientific knowledge.
Although the other parts of the scientific endeavour are in fact influenced by worldviews of different sorts, worldview influences on science are the most problematic.

Our contentions is simple: theories should be accepted by the scientific community only in the light of considerations that involve transparent and reproducible empirical data, other (accepted) theories, and cognitive values such as consistency, simplicity, and explicatory power. Worldview (political and ideological) considerations but also appeals to authority, consequences, force, and popularity—to name some argumentation fallacies—are illegitimate ways of deciding between theories. These undermine the integrity of science. Our basic tenet is that one does not have to agree on what constitutes a good human life, a good society, what a righteous societal order is and et ceteras. As is clear for instance in Douglas and Wildavsky’s work on the issue of risk, and also in the philosophical work of Fleck and Kuhn, normative (worldview) considerations nevertheless play an integral role in the justification phase of science. In the table form presented below, Stenmark portrays the scientific enterprise—science in relation to worldview influences as follows with which we fully concur:

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<thead>
<tr>
<th>Table 1 Science and worldviews</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worldview-Neutral Science</strong></td>
</tr>
<tr>
<td>Problem-stating phase</td>
</tr>
<tr>
<td>Development phase</td>
</tr>
<tr>
<td>Justification phase</td>
</tr>
<tr>
<td>Application phase</td>
</tr>
</tbody>
</table>

Obviously, the extent to which worldviews shape the scientific process is not encapsulated in this scheme. Nonetheless, we are convinced that few scientists today seem to be conscious of the effects of various worldviews on the scientific questions asked, the generation of empirical data and on the formulation and assessment of theories. This is not necessarily a bad thing, yet needs to be considered carefully. Especially at the justification phase (science), worldview influence could well distort the process of science. With this framework of science, toxicological research, its axioms and its research modus (e.g., high-dose research low-dose extrapolation) can be understood more comprehensively. It also shows that the choice of toxicological models is not just a matter of science but also a matter of worldviews, which, however, would interfere most unfortunately within the realm of science.

The status of knowledge as an autonomous entity and its relation to the issue of power are elements, which surface in precautionary culture most noticeably. For that reason we will now turn to the characteristics of this culture.

**A Concise Description of the Rise of Precautionary Culture**

It is by now common to note that industrial society has changed into risk society. In 1986 Beck coined the concept of the risk society. Beck’s basic idea is that industrial society has developed to such an extent that the distribution of scarce goods is no longer the primary social problem. The main problem is the distribution of the technological risks that are a product of the industrial system of production and the commercial exploitation of scientific knowledge. It is this problem that the fundamental social struggles are fought about in the risk society. One of the effects of this change in the subject of social struggle, Beck predicted, is that people will increasingly demand the politisisation and democratisation of the worlds of science and industry.

Some twenty years later there is little doubt that Beck came up with some very insightful observations and predictions. Major issues in today’s Western society indeed centre on safety and security. In risk culture there is a constant drive to identify new risks. Whether induced by legislation or court decisions, the routine response to risk is to establish an insurance or compensation scheme. This trend has accelerated in all modern societies, especially after WW II, and resulted in some version of the welfare state. This historical development encapsulates a number of collective experiences of civilians of Western society. These lessons were institutionalised in what we now call precautionary principle.

A major lesson, first, is that social institutions are not beyond reproach. All modern societies show a loss of trust in its main institutions. (We will leave aside the sociological intricacies, and refer to some work on this issue.) Especially relevant is the erosion of the classic and related modern ideals of autonomous knowledge and autonomous law. When the idea of absolute objective scientific truth was substituted with the notion of inter-subjective knowledge, it became only a matter of degree to take this criticism further and claim that all knowledge is directly related to interests and power. Agreement on both facts and values have become an integrated whole. Scientific findings therefore a not judged as autonomous knowledge of reality, but scrutinised and valued in relation to the social structures it appeals to or is regarded to be in conflict with.

A second lesson learned is that increasingly, incurred damage is being compensated. In fact, the more damage is compensated for and even prevented, the more this becomes the standard. Modern man has created a legal culture in which ‘individual rights’ are constantly being created and augmented; a process that seems to be driven by the idea of total justice. This kind of legal culture is common to all modern societies.

A third and closely related learning process has to do with the fact that modern societies have gradually become much more safe. The simple fact that modern man lives approximately twice as long than their great grandparents is telling. It fits the logic of risk culture that the extension of compensation goes hand in hand with the extension of prevention. In this regard we could speak of the moral value of economic rationality. Ironically the safer human life in modern society becomes, the more civilians tend to feel threatened by the remaining risks. The status quo of the achieved high standard of living in
the Western world is thereby directly the publicly desired outcome of numerous types of regulation on all regulatory fields. Public reluctance towards regulatory attenuation is therefore a common feature of Western precautionary culture. Western society has become increasingly risk averse.

The Precautionary Principle and its Flaws

These social changes that have resulted in precautionary culture are most notably expressed legally in the precautionary principle. As Ellman and Sunstein mention in the latest Belle Newsletter, the precautionary principle has come to enjoy widespread international support. This precautionary principle is a principle of international law, which was first developed during the 1970s and 80s but became more and more important during the 1990s. Its status as a firmly established principle of international law is however still hotly debated. The precise content and meaning and therefore the best way to formulate the principle are also still a matter of intense dispute. Whatever the definition, the basic precept of the precautionary principle is that with its implementation it will reduce or even eliminate a certain target risk.

To take precautionary measures as such is, however, not a new phenomenon. On the contrary, it is defined and institutionalised in modern day society in e.g. insurance companies and lawmaking. This institutionalisation was the result from knowledge of the causal hazard chain. Precautionary thinking, however, seeks to go beyond the causal hazard chain as is shown by the fact that the principle is usually invoked when scientific knowledge concerning a specific (environmental) risk is deficient or even lacking. As the Rio definition—regarded as the most authoritative among the many formulations of the precautionary principle—reads: ‘… 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.’ This description of precaution is also known as the triple-negative definition: ‘not having scientific certainty is not a justification for not regulating.’

The principle is presented as a way of handling modern risks, and is said to promote prevention, rather than cure. In essence the precautionary principle seeks to advance the timing and tighten the stringency of ex ante regulation. On these sliding scale dimensions, regulation is ‘more precautionary’ when it intercedes earlier and/or more rigorously to preclude uncertain future adverse consequences of particular human activities. The axiom put forward by the precautionary principle is that implementation regarding risks to human health and/or the environment singularly results in the reduction or elimination of those risks. However, Stone notes that the precautionary principle has been put forth ‘in so many versions, often with cognate phrasing, as to belie the pretensions of the definite article.’ As the precautionary principle advances into law, he argues, ‘it is increasingly frustrating that there is no convergence either as to what it means, or as to what regions of action (environment, public health), it is supposed to apply.’

One obvious quandary in the common definition of the precautionary principle holds that it seeks to impose timely protective measures to prevent uncertain risks, i.e. risks as to which there is little or no data on their probability and magnitude. That aspiration, however, is unachievable due to a problem common to effectively all formulations of the precautionary principle. From a logical point of view the Rio definition is meaningless, because the lack of scientific certainty deprives us of the possibility to calculate the costs and benefits of precautionary measures. Therefore, the principle makes more than half blind. It encourages a very partial asymmetric view of reality by focusing only on certain risks one wants to avoid. The costs of avoidance are assumed to be zero, which is clearly not the case. Indeed, considerable scientific evidence suggests that expensive regulation targeted at a specific risk has adverse effects on human life and health (the so-called cost-induced fatalities). It is by no means precautionary to induce morbidity and mortality as a result of regulatory expenditure (that might subsequently also generate opportunity costs) as a result of which citizens incomes decline.

Therefore, the principle by definition leads in no direction whatsoever. The reason is that risks (and its costs) of one kind or another are on all sides of the regulatory and societal equation, and it is therefore impossible to avoid running afoul of the principle. The precautionary principle seems to offer guidance only because people blind themselves to certain aspects of the risk issue, focusing on a mere subset of hazards. This means that despite the fact that precaution by definition cannot give guidance, a safe direction (position) is assumed when implementing the principle, whereby it is seemingly made operable. The chosen direction postulated to be the route to safety is however imposed deus ex machina, in a hidden way, and by implicit assumption that the chosen direction is a matter of necessity and common sense.

Analysed at this fundamental and logical level, the precautionary principle engenders an impossible arrangement: to decide on a ‘safe course’ results in the formation of other new unknown risks, which,
by definition, evokes a secondary precautionary response, \textit{ad infinitum}. To break this infinite regress one can only limit the application of precaution. Precaution therefore demands choice. One cannot be cautious on all fronts, as this would completely stifle any type of activity including precautionary policy itself. By capriciously selecting some target risk and focusing exclusively on that risk, regulators can construct a decision as to the proper course of action. Application of the precautionary principle ‘guided’ by this approach involves random choices of risks and results in policies that are blind for the negative external effects thereby created.\textsuperscript{38}

One concluding assertion is that within the precautionary context described above, the assessments and policies within the chemicals field are primarily focussed on secondary risk management. Regulators and (scientific) experts alike are being made increasingly accountable for what they do and thereby are becoming increasingly preoccupied with managing their own risks. Particularly, secondary risks to reputation are becoming as significant as the primary risks for which policies should in fact be devised.\textsuperscript{39} The increasingly dominant regulatory culture of risk-aversion\textsuperscript{40} therefore engenders a policy culture that is best served with a linear approach to toxicity. An example of this (arbitrary) risk approach is the exclusive focus on the miscellany of man-made chemicals under the EU’s REACH program, with which a ‘toxic-free’ society (meaning a societal and natural environment measurably free of man-made chemicals) is envisaged.\textsuperscript{41} We will discuss REACH below.

\textbf{The Position of Science in Precautionary Culture}

When scrutinising the position of scientific knowledge in precautionary culture, it is clear that a profound ambiguity towards scientific knowledge exists.\textsuperscript{42} Precautionary culture, thus, typically shows strong scepticism with regard to the knowledge claims of science. By its nature, scientific knowledge is never complete and certain, which for proponents of precaution would offer the best criteria for the implementation of the precautionary principle. (In a decade or two, science will unquestionably have developed new and surprising insights.) This scepticism is very strongly developed in post-modern theories of science, where all knowledge is presented as ‘socially constructed’\textsuperscript{43}. It is denied that ‘reality’ offers us an objective point of reference to decide on the value of conflicting theories.\textsuperscript{44} Science cannot claim a privileged position, as ultimately even scientific knowledge is just another social construction of reality.\textsuperscript{45} Knowledge and power are regarded to be wholly interdependent, whereby even science,\textsubscript{3} –as part of the framework of science- cannot escape worldview influences.

This scepticism, however, is only half the story. Indeed, the reverse of the precautionary stance towards the scientific endeavour and its potential and mandatory results is optimistic to the same extent as it is pessimistic. The goal of precaution is ‘to foresee and forestall’.\textsuperscript{46} In order to seriously entertain this conviction and the concomitant goal of preventing future damage from happening, one needs a strong belief in what science can and must deliver. A very good example of this incongruous attitude towards science we for instance find in the words of Raffensperger and Tickner:\textsuperscript{47}

‘Scientific uncertainty about harm is the fulcrum of this [precautionary; authors] principle. Modern-day problems that cover vast expanses of time and space are difficult to assess with existing scientific tools. Accordingly we can never know with certainty whether a particular activity will cause harm. But we can rely on observation and good sense to foresee and forestall damage.’

At first sight, this quote –exemplary for precautionary culture- states that even when we need to be sceptical about what science has to offer, we still can be optimistic because of observation and good sense. However, when we consider these alternatives carefully we find that they are the basic tenets of the investigative attitudes that led to the development of science and the ideal of objective knowledge in the first place. Unwittingly the authors return to the very same thing they discard in the first place. So in precautionary culture, a very high level of scepticism with regard to what science cannot do, goes hand in hand with a very high level of confidence regarding what science is expected to deliver. In this situation, the line between real risk and mere conjecture may be practically imperceptible. Although the aid of science is enlisted, science is deemed insufficient to deliver discerning criteria. Such is the position of science in precautionary culture.

\textbf{Hormesis and the Choice of Default Models}

The predicament of scientific evolution in precautionary culture –as discussed above- is well illustrated in the EPA quote at the beginning of our article. On the one hand it is recognised that adaptive responses could well be a reality and scientific progress will undoubtedly elucidate this issue more fully; on the other hand current and future knowledge on hormesis is ignored as an assumed principle of safety and will therefore not be part of the EPA risk assessment methodology. This EPA position is in a similar fashion reflected by Page:\textsuperscript{48}

“When a regulator makes a decision under uncertainty, there are two possible types of error. The regulator can overregulate a risk \textit{[false positive, author]} that turns out to be insignificant or the regulator can underregulate a risk that turns out to be significant. If the regulator erroneously underregulates \textit{[false negative, author]}, the burden of this mistake falls on those individuals who are injured or killed, and their families. If a regulator erroneously overregulates, the burden of this mistake falls on the regulated industry, which will pay for regulation that is not needed. This result, however, is fairer than setting the burden of uncertainty about a risk on potential victims.’

This position is classical asymmetric and typical for precautionary culture: it assumes what actually should be proven, namely, that the health effects of an assumptive over-regulatory approach would be superior to the alternative. The concomitant assumption is that there
are no health detriments from proposed overregulation. Page presents a choice between health and money or even health with no loss whatsoever, as a peripheral presumption is that industry will find a better and a cheaper as well as safe way. Something (health) is gained with nothing lost (no adverse health effects from over-regulations).59

The position proposed by Page would, in the case of the EPA position on hormesis, make sense only when (1) over-regulation in terms of public and environmental health would indeed be measurably superior to under-regulation, and (2) that in the face of uncertainty ignoring hormesis is the ‘safe’ option.50 Both stances are to be found in the EPA risk assessment document, where issue (1) is addressed under the term ‘conservatism’, and issue (2) –the main topic of this paper- portrays the precautionary deus ex machina inference of guidance. These two topics are very much related. As the EPA states (p. 11 – 12):

‘Because of data gaps, as well as uncertainty and variability in the available data, risk cannot be known or calculated with absolute certainty. Further, as Hill (1965) noted, a lack of certainty or perfect evidence ‘does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.’ Therefore, consistent with its mission, EPA risk assessments tend towards protecting public and environmental health by preferring an approach that does not underestimate risk in the face of uncertainty and variability. In other words, EPA seeks to adequately protect public and environmental health by ensuring that risk is not likely to be underestimated. However, because there are many views on what ‘adequate’ protection is, some may consider the risk assessment that supports a particular protection level to be ‘too conservative’ (i.e., it overestimates risk), while others may feel it is ‘not conservative enough’ (i.e., it underestimates risk). This issue regarding the appropriate degree of ‘conservatism’ in EPA’s risk assessments has been a concern from the inception of the formal risk assessment process and has been a major part of the discussion and comments surrounding risk assessment.’

The EPA document clearly chooses not to underestimate risk in order to—as they put it- protect public and environmental health. Over-regulation is therefore clearly favoured over under-regulation, although different views exist on what these terms exactly mean. Incorporating hormesis is -as it shows- regarded by the EPA as potentially resulting in an underestimation of risk. This is however postulated without proper scientific evidence; the path towards safe regulation is inferred a priori and results in the choice of default toxicological models, namely the linear threshold (LT) and non-threshold (LNT) models that are regarded as the overarching risk paradigm in regulatory culture. In terms of the over-regulatory bias, the choice to ignore hormesis seems logical and very much in line with precautionary culture.51 However, as risks and costs are on all sides of the societal and regulatory equations, the choice of threshold and nonlinear default models as a precautionary basis of regulation in the face of uncertainty and ignorance is the result of the deus ex machina inference of guidance. Parenthetically, it is ironic that the EPA chooses to quote on the disregard of knowledge, while ousting the concept and the knowledge of hormesis from its risk assessment procedures without a proper rational.

In the Belle Newsletter of March 2004, Griffiths—in his response to Hammit- gives some insight in the (public) reluctance towards hormesis, which is in line with what we have put forward on precautionary culture in relation to knowledge and power:52

‘On the surface, the results of determining that a substance displays hormesis seem relatively uncontroversial. If the hormetic exposure-response curve is steeper than the linear curve, then the marginal benefits of reducing exposure are greater than under the linear model, and the optimal regulatory level is more strict. If the hormetic curve is flatter, then the detrimental effect of a substance is substantially less than that implied by the linear curve. In other words, hormesis appears to imply stricter regulation or less harm. Most government economists, though, know that regulatory decisions are (and should be) made including factors other than the economically optimal level. One of these factors is public concern, and there seems to be some public reluctance to assuming hormesis.

There are a number of possible reasons for this public concern. One possibility is that determining a substance to be hormetic will always imply a lower level of risk for any given exposure. One might argue that precaution dictates that we default to a model that produces the highest level of risk. Assuming a linear model when hormesis is valid, however, raises Portney’s (1992) ‘happyville’ problem, where the government must decide whether to regulate a chemical that is of public concern but, in fact (according to risk assessors), poses no real risk. The benefits of regulation in such a situation are unclear.

Another possible concern is that assuming hormesis will weaken regulatory standards. As pointed out above, this is not necessarily true. The optimal level could be more strict under hormesis if the slope of the hormetic curve is steeper than the linear curve. … The real concern is where the optimal regulatory level under hormesis is less strict than the linear no-threshold model, the region where the hormesis curve is relatively flat.

It shows that the scientific position of hormesis is no more an autonomous debate within the realm of the scientific arena. Although it seems to us to be quite clear that the implications of hormesis lie outside the fields of toxicology and pharmacology—despite the fact that numerous toxicological research efforts are needed to further elucidate the issue of hormesis- the critics of hormesis will be mainly outside the scientific arena.'
Hormesis, Oxygen and Chemicals Regulation

The question in what way high dose and low dose exposures relate to each other is a longstanding one. The age-old Paracelcus axiom ‘Sola dosis facit venenum’—the dose makes the poison—does not address the shape of the curve linking both ends of the exposure scale. For the sake of simplicity two main toxicological linear models will be mentioned here. Model A depicts the ‘no-dose no-illness’ approach when dealing with genotoxic carcinogens. The fact that chemicals are capable to react with hereditary material—thereby potentially inducing carcinogenesis—makes the assumption that even one molecule might in theory generate cancer seemingly viable. Model A is usually referred to as the LNT model (Linear Non-Threshold model). Model B assumes a threshold in the dose-response curve. So below the threshold the toxin is assumed not to generate any harmful effect in the exposed organism. Non-carcinogens are thought to usually exhibit such behaviour. Model B is usually referred to as the LT model (Linear Threshold model).

Model C is usually referred to as hormesis. Hormesis is in many ways the physiological equivalent of the philosophical notion that ‘what won’t kill you, will make you strong’. Hormesis is best described as an adaptive response to low levels of stress or damage (from for example chemicals or radiation), resulting in enhanced robustness of some physiological systems for a finite period. More specifically, hormesis is defined as a moderate overcompensation to a perturbation in the homeostasis of an organism. The fundamental conceptual facets of hormesis are respectively: (1) the disruption of homeostasis; (2) the moderate overcompensation, (3) the re-establishment of homeostasis; (4) the adaptive nature of the overall process. In the above-depicted figure, U-shape C illustrates this.

Hormesis epitomizes whichever benefit gained by the individual organism from resources initially allocated for repair activities but in excess of what is needed to repair the immediate damage. This advantage could also pre-adapt the organism against damage from a subsequent and more massive exposure within a limited time frame. Therefore, the overcompensation response may satisfy two functions: the assurance that the repair was adequately accomplished in a timely fashion and protection against subsequent greater insult. Possible mechanisms are multiple: enzymes that repair damaged DNA, stimulated immune responses, apoptosis that eliminates damaged cells that would otherwise become cancerous and the like.

We need to define hormesis in a continuum of the dose-response curve. There are low-dose effects and high-dose effects of exposed organisms. Low doses are stimulatory or inhibitory, in either case prompting living organisms to be dissociated from the homeostatic equilibrium (steady state) that in turn leads to (over)compensation. For example, heavy metals such as mercury prompt synthesis of enzymes called metallothioneins that remove toxic metals from circulation and probably also protect cells against potentially DNA-damaging free radicals produced through normal metabolism.

High doses push the (researched) organism beyond the limits of kinetic (distribution, biotransformation, or excretion) or dynamic (adaptation, repair, or reversibility) recovery. The latter response is the classical toxicological object of research usually required as a result of regulatory concerns (regardless of the toxicological endpoint under scrutiny) whereby hormetic responses are by default regarded as irrelevant and therefore unlooked for. Indeed, regulatory driven hazard assessments focus their primary, if not exclusive attention, on the higher end of the dose-response curve in order to estimate the NOAEL and LOAEL levels modelled with linear assumptions. This is the default position (more or less) taken for granted, and could be appropriately referred to as the toxicological risk paradigm. In the Kuhnian tradition this means that toxicological research as mentioned in this paragraph is the standard research model—with all its tacit knowledge—applied for numerous decades now. All ensuing work—especially in relation to science and science—is done within the conceptual framework developed there from.

Figure 1 Three toxicological models

Despite the evidence on hormesis generated over the years, the question remains to what extent hormesis is a general feature of life. Quite a few recent studies note, however, the pervasiveness of hormesis in toxicology. Some hormetic effects are quite multifaceted, and will therefore have a clear bearing on regulatory policy and questions precaution in its historic framework. While some evidence implies that dioxin suppresses breast tumours at low doses, studies have also shown that small amounts of dioxin can promote liver tumours; only when all tumours are taken into account do the dioxins exhibit a U-shaped curve. Cadmium fits this profile as well; small doses could show to reduce some forms of cancer, yet similarly might promote other forms of cancer. A similar type of complexity has been unearthed for some anti-tumour agents that inhibit cell proliferation at high doses, where they may be clinically effective, become like a partial agonist at lower doses, where they augment cell proliferation.
So, the straightforward beneficial – adverse dichotomy is not implied per se by the term hormesis. Therefore, we will turn to oxygen.

**Oxygen**

The concept of hormesis, its pervasiveness and its subtle context and implications are, however, in our view illustrated brilliantly with the evolutionary dose-response relation towards oxygen. Around 3500 million years ago, intense solar radiation bombards the surface of the earth and anaerobic life begins. It is assumed that 2500 million years ago, oxygen is gradually released from water by blue green algae. Oxygen levels in the atmosphere reach 1% and more complex cells with nuclei (eukaryotes) begin to evolve 1300 million years ago and multicellular organisms emerge. Around 500 million years ago, oxygen levels in the atmosphere reach 10%. The ozone layer protects against the UV light and facilitates the emergence of life forms from the sea. Primates appear 65 million years ago. Humans appear 5 million years ago and the atmospheric oxygen levels reach 21%.

Evolutionary adaptation to the slow appearance and increasing atmospheric concentration of oxygen is impressive. Anaerobic life forms had to adjust to this toxic compound. The fascinating adaptation that occurred during this chemical evolution has been sketched for the reducing protein cytochrome P450 present in anaerobic life forms. Cytochrome P450 has probably been present in living organisms before the advent of free oxygen and before the development of other respiratory hemoproteins. This view is strengthened by the finding that cytochrome P450 can catalyze the reductive metabolism of a variety of compounds, particularly under anaerobic conditions. As a defence for the anaerobic life forms against oxygen, cytochrome P450 reduced the oxygen toxic at atmospheric concentrations. Later this mechanism could favourably be employed by aerobic life forms because the reactivity of the reduced oxygen was used to oxidize xenobiotics. In this way lipophilic xenobiotics could be transformed into more water-soluble oxidized metabolites, which are easier to excrete than the parent compound. The evolutionary age old cytochrome P450 might explain its wide occurrence throughout the phylogenetic scale. The importance of cytochrome P450 in the biotransformation of both endogenous and exogenous compounds is further underlined in mammals where the enzyme has been found in very divers organs and tissues. The evolutionary toxic response to increasing oxygen levels thus slowly turned into a protective mechanism (a decrease in toxicity) because oxygen is employed to metabolize a wide variety of lipophilic compounds.

It is common knowledge that lungs are used by aerobic life forms for the uptake of oxygen in the blood. On the other hand, oxygen can be reduced enzymatically to form reactive oxygen species like superoxide anion radicals, hydrogen peroxide or hydroxyl radicals. Not only cytochrome P450 uses these reactive oxygen forms but also oxidases located on phagocytic cells employ these reactive oxygen species to destroy invading micro-organisms. An overflow of these reactive oxygen forms may overwhelm the physiological enzymatic and non-enzymatic protection, which may lead to damage. The excessive generation of reactive oxygen species is associated with many disorders. Lung diseases for example like asbestosis, silicosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, cystic fibrosis and chemical (paraquat, bleomycin) induced lung toxicity have been related to the toxicity of oxygen. Oxygen need and oxygen-induced damage thus clearly form a biphasic toxic response.

Protection against the damaging effect of reactive oxygen species is formed by an elaborate enzymatic and non-enzymatic antioxidant network. One of the enzymatic protective agents is superoxide dismutase (SOD). We have recently established a good protective effect of lecithinized Cu,Zn-superoxide dismutase (SOD1) against the doxorubicin-induced cardiotoxicity. These experiments were performed reluctantly, because it is known that SOD1 generates hydroxyl radicals when it is incubated with hydrogen peroxide. With EPR experiments the formation of hydroxyl radicals was established. The CuZn-SOD comprises a positively charged channel that ends near the active site at the Cu-ion. This channel conducts the substrate superoxide anion radical, which also explains the high rate for the dismutation reaction. The Cu-ion in SOD1 probably catalyses a Fenton-like reaction that yields hydroxyl radicals and leads to inactivation of the enzyme. We published that at relatively low concentrations of SOD1 the superoxide anion radical is scavenged effectively, whereas at higher SOD1 concentrations hydroxyl radicals are formed. This forms a striking SOD concentration dependent U-shaped protection curve against the toxic response to superoxide anion radicals. It implies the use of an optimal SOD concentration as protective therapeutic protein.

Also non-enzymatic antioxidant supplements are often recommended to preserve or regain good health. Of the dietary antioxidants, flavonoids have received much interest. A prominent flavonoid is quercetin, a good inhibitor of the reactive oxygen species-induced lipid peroxidation. Interestingly, the oxidation product of quercetin, which per definition arises after the compound displayed its antioxidant action, is again reactive. This oxidation product is an ortho-quinone or the tautomeric quinone methide, which reacts with thiols. In other words, the inhibition of lipid peroxidation (i.e. protection) leads to a thiol reactive metabolite (i.e. damage). Also in this case a biphasic response is to be expected. In order to optimize supplementation with enzymatic and non-enzymatic antioxidants we need on the one hand to improve our knowledge on the biphasic dose responses to reactive oxygen species and on the other hand on the biphasic protection by antioxidants like SOD or flavonoids per se.

On a more general concluding note, the best strategy to boost host defence mechanisms that are known to be activated in response to oxidative stress seems to be stress itself in line with the concept of hormesis. That is, a sub-lethal or conditioning stress can lead to improved survival and reduced tissue damage following a subsequent, more severe stress.

Considering the above, it is essential, in our view, to go beyond toxicology and pharmacology itself, as the major implications of hormesis.
–apart from its highly interesting and worthwhile academic traits– lie outside toxicology. As Stebbing notes:75

‘If the validity of the homeostatic hypothesis is confirmed, then it becomes a necessity to incorporate some fundamental implications and applications of hormesis (e.g., risk assessment) into toxicology. At this stage, it is not surprising that mainstream toxicology has marginalized hormesis, because it now requires the physiological disciplines to validate the phenomenology with an explanation, because without it hormesis as a concept is of dubious worth. While hormesis is a toxicological phenomenon, its further explanation lies beyond the discipline that has brought our understanding to its present level.’

Therefore we propose to look at two examples where basic default assumptions driven by the default precautionary approach could very well be attenuated and rationalized by means of broadening the viewing screen. The basis lies in the concept of hormesis itself –‘the molecular level’ and the organism’s response to the toxicological (pharmacological) perturbation- and the interaction of that knowledge with the economics of regulation. Subsequently, the EPA assumptions on hormesis will be reviewed.

REACH

A European example of the linear non-threshold regulatory approach with specific precautionary connotations is REACH.76 On May the 7th, 2002, Environment Commissioner Wallström and Enterprise Commissioner Liikaaen presented a draft proposal for a new and revolutionary chemical Regulation known as ‘REACH’, an acronym that stands for ‘Registration, Evaluation, and Authorization of Chemical Substances’. REACH is one of the most important EU legislative initiatives in recent years. The draft Regulation, which would replace over 40 existing directives and regulations, would implement the proposals set out in the Commission’s White Paper on the Strategy for a future Chemicals policy, and involve a major overhaul and expansion of the EU’s chemical legislation. The draft Regulation is a response to demands by environmental NGO’s and green political parties. They have argued that existing chemicals, which would constitute 99% of the total volume of chemicals used in Europe, create unknown risks to human health and the environment. Commissioner Wallström has called this ‘an unacceptable knowledge gap’, and lamented that ‘we are unwittingly testing chemicals on both living humans and animals’. The Commissioner also faults the present ‘new’ chemicals regulatory system because government assessments have been slow and because it does not encourage innovation. Her proposed solution to these problems is the REACH regime.77

Costs estimates –scientific, regulatory and economic– for implementing REACH vary wildly; up to a 100 billion euro has been suggested. The European Commission estimates the costs to be 50 billion euro. There is now way of telling what the actual costs will be, yet the benefits have been estimated by the European Commission to be several thousand (statistical) human lives in Europe as a result of diminished environmental exposure to synthetic chemicals based on the default assumptions of the LNT (and LT) models.

The REACH regime is viewed as the way to a ‘toxic-free’ society or, to the extent that is unachievable, at least to a society that optimally reduces the risks arising from chemicals. REACH seems to have been inspired on Rachel Carson’s book ‘The Silent Spring’, which held synthetic chemicals responsible for what was perceived as an increasingly unhealthy, unsafe, and unnatural world.78 It also reflects a profound belief in the kind of technocratic social engineering endorsed by the Club of Rome in its report ‘The Limits to Growth’.79 To establish a ‘toxic-free’ society, the draft regulation would create an unprecedented level of government control over the manufacture and use of chemicals as substances, in preparations, or in so-called ‘articles’, i.e. all products that are not substances or preparations. As noted, the REACH regime is intended (1) to close the alleged ‘knowledge gap’ with regard to existing chemicals, i.e. those that were on the market as of 1981 and are listed in the EINECS (European Inventory of Existing Chemical Substances), and (2) to control environmental and health risks arising from chemicals in products, ranging from carcinogens to endocrine disruption said to be caused by phthalates used as softeners in PVC plastics.80 In designing the new system, the responsible Commissioners have been guided by the precautionary and substitution principles.

A number of issues stand out in the basics of REACH. The idea, first, that a ‘toxic-free’ society is a society without the environmental presence of synthetic chemicals is a striking expression of precautionary thinking in which all the flaws discussed above surface. The application of precaution in REACH is without rational limited to synthetic chemicals and the route to presumed safety is an envisioned ‘toxic-free’ society, meaning a society where synthetic chemicals are absent from the environment. REACH has in effect extrapolated the functionality of the classical LNT model to a societal level and has interpreted the model to mean that any exposure to any synthetic chemical is dangerous. Indeed, it is regarded as anathema that humans and animals are exposed to synthetic chemicals at all, in which ‘green thinking’ is expressed unreservedly.81 A moral dichotomy between natural versus synthetic is thereby introduced. This idea—paradoxical—has been fed by the technological advances in the analytical field. Numerous labs in the world now routinely scan numerous synthetic chemicals in the environment that could not be detected some ten years ago. The ‘visibility’ of synthetic chemicals in the environment and even the human body has been enhanced dramatically as a result of technological innovation.82

It is clear that REACH is in part a product of the serious misreading of the word ‘toxic’ whereby the regulatory acceptance of hormesis is seriously hampered, as Stebbing notes.83 ‘Toxicity is a function of the concentration resulting from exposure rather than the properties of the causative agent itself. Reference to (especially synthetic) chemicals as ‘toxins’ implies that the predominant properties of those chemicals are their toxicity, when in truth it is a limited range of concentrations that determines toxicity. Accordingly, supposedly harmless agents will
show toxicity at high enough concentrations, while agents that show toxicity at low concentrations may be harmless at still lower concentrations. So the term ‘toxic chemical’ is logically flawed and leaves no room for recognizing that a certain concentration of such a chemical is nontoxic, while other concentrations may even be hormetic.

The acceptance of hormesis would in principle seriously attenuate the basics and ambition of REACH, especially the utopian ‘toxic free’ society. Despite the fact that REACH is specifically driven by precaution, in light of hormesis the precautionary principle itself does not justify the entertained default assumption at all. The LNT model is both compelled by the principle and at the same time forbidden by it. Compelled because of the possible risk of harm at low levels; forbidden because of the possibility of benefit at low levels (and hence the possibility of harm from eliminating low levels of exposure). There is no reason to focus only on the risks of inaction and to neglect the risks of action. Negative external costs of regulation are part and parcel of reality irrespective of regulatory interest and focus. The reality of hormesis shows that REACH—once implemented—is far from precautionary, on the contrary.

The precautionary REACH approach encourages people to think that a ‘safe’ toxic-free environment is within reach as a result of governmental regulatory involvement. A toxic-free environment, however, does not exist and is a contradiction in terms, and, counter-intuitively, would likely not be safe, but, on the contrary, expose us to higher risks. REACH oversimplifies the world and thereby misleads civilians and misguides regulatory action. With the REACH program, synthetic chemicals are indicted as major threats to human health and the environment, which they are not. The precautionary principle is made operative because regulators blind themselves to many aspects of the situation and focus on an extremely limited subset of the risks at stake. Moreover, the precautionary direction towards safety is assumed without rational. If hormesis is to be regarded as the most fundamental description of the relation between dose and response, the LNT model is not precautionary at all.

Yet, policymakers and regulators in Europe would not look upon that favourably with its track-record of precautionary bias. Governments must decide whether to regulate chemicals according to the REACH-rational—whereby mostly public concern is addressed—where the actual risks of exposure will be quite different. Stringency in relation to chemicals is however publicly regarded as a health and safety prerequisite in modern society, and from a bureaucratic point of view addresses secondary risk issue of liability and reputation most effectively.

This prerequisite has however very little to with the actual risks chemicals pose to public health. The hormetic toxicological approach revolutionizes the strategies and tactics used for risk assessment, management and communication of toxic substances. Regulatory and/or public-health agencies in most parts of the Western world have edified the public in the past decades to expect that there may be no safe exposure level to many toxic agents, especially carcinogens.

REACH is an expression of this assessment, management and communications paradigm. If the hormetic perspective were accepted, the risk-assessment message would have to change utterly. It would certainly be resisted by many regulatory and public-health agencies and obviously the environmental NGOs—in line with what we have said about precautionary culture—as an industrial-influenced, self-serving scheme that could, however, lead to less costly clean-up standards with a much higher cost-effectiveness, especially in relation to public health, yet retain its protective goals in, however, a much more comprehensive way.

Chloramphenicol

A second example deals with the issue of veterinary residues in food that do not have a MRL (Maximum Residue Limit). The detection in 2001 of chloramphenicol, a broad-spectrum antibiotic (‘CAP’) still used as human medication (mostly ophthalmic use) yet forbidden as a veterinary drug, in shrimp imported into Europe from Asian countries was presented as yet another food-scandal. The initial European response was to close European borders to fish products, mainly shrimp, from these countries and make laboratories work overtime to analyse numerous batches of imported goods for the presence of this antibiotic. Some European countries went so far as to have food products containing the antibiotic destroyed. This regulatory response spilt over to other major seafood-importing countries such as the United States.

The legislative background to their response is to be found in Council Regulation EEC No. 2377/90, which was implemented to establish maximum residue limits of veterinary medicinal products in food-stuffs of animal origin. This so-called ‘MRL Regulation’ (maximum residue limit) introduced Community procedures to evaluate the safety of residues of pharmacologically active substances according to human food safety requirements. A pharmacologically active substance may be used in food-producing animals only if it receives a favourable evaluation. If it is considered necessary for the protection of human health, maximum residue limits (‘MRLs’) are established. They are the points of reference for setting withdrawal periods in marketing authorisations as well as for the control of residues in the Member States and at border inspection posts.

Council Regulation EEC No. 2377/90 contains an Annex IV, listing pharmacologically active substances for which no maximum toxicological levels can be fixed. From a regulatory point of view any exposure to these compounds is deemed a hazard to human health. These substances are consequently not allowed in the animal food-production chain. So-called zero tolerance levels are in force for Annex IV. CAP—and other Annex IV substances—should not be detected in food products at all, regardless of concentrations. The presence of CAP in food products, which can be detected by any type of analytical apparatus, is a violation of European law and moreover deemed to be a threat to public health. In consequence, food containing the
The zero tolerance approach for Annex IV compounds applies the precautionary principle to food safety issues as the simple heuristic: ‘when in doubt, keep it out’. The explicit goal of zero tolerance is not risk-based but precaution-based, as the absence of a MRL is from a regulatory point of view translated as ‘dangerous at any dose’. Incidentally, in the case of CAP no ADI could be established for lack of scientific data, and not because of extraordinary toxicological characteristics. The smallest amount of these residues is considered unfit for human consumption. For all intents and purposes, zero tolerance is best understood as zero concentration. Only when Annex IV substances are completely absent from food (at zero concentration) the risks are deemed completely absent. Technological analytical innovation had become the driver of zero tolerance policies and subsequently and not surprisingly generated a serious regulatory impasse. (Parenthetically, the Second Law of Thermodynamics nullifies zero tolerance policies, as zero-concentration—as implied by zero tolerance—is not a physico-chemical reality.)

The concept of hormesis could seriously ameliorate this situation simply because striving for absence of a certain chemical both from a regulatory and more importantly from a public health perspective is altogether unnecessary and even counterproductive.

Again, the assumption ‘dangerous at any dose’ in relation to exposure to CAP is related to the use of the LNT model. Toxic effects of CAP exposure have been observed—albeit only as a result of therapeutic exposure—of which aplastic anaemia and leukaemia are the most important. The total aplastic anaemia incidence is estimated in the order of 1.5 cases per million people per year. Only about 15 per cent of the total number of cases was associated with drug treatment and among these CAP was not a major contributor. These data gave an overall incidence of therapeutic CAP-associated aplastic anaemia in humans of less than one case per 10 million per year. In considering epidemiological data derived from the ophthalmic use of CAP, systemic exposure to this form of treatment was not associated with the induction of aplastic anaemia. There seems to be no evidence whatsoever that low-level exposure to CAP, either as a result of ophthalmic use or of residues in animal food, is related to aplastic anaemia.

When considering the difference between therapeutic exposure—as a result of which aplastic anaemia has been observed, albeit rarely—and exposure as a result of food residues—as a result of which aplastic anaemia has never been observed—it is clear that CAP does not present any hazard. The food residue exposure levels shown in Figure 2 are taken from the RIVM study (Dutch National Institute for Public Health and Environment) on CAP in shrimp.

Figure 2: CAP exposure level differences between therapy and food residues

Again, the commentary by Stebbing on the semantic misconceptions of the word ‘toxic’ is in order here. The concept of hormesis would seriously assuage the misguided zero tolerance regulatory approach (apart from the fact that zero-tolerance as a legal concept is unlawful). Again, the precautionary principle directs the belief that a LNT model would be the most protective of human health. As with the REACH objective of a ‘toxic free’ society, zero tolerance for veterinary substances without a MRL has the goal of ‘toxic free’ food and expresses a precautionary regulatory culture blind for negative external policy costs, and self-limiting in relation to the best available science.

As a matter of contemporary history, the days of the zero tolerance approach in food regulation seem to be numbered simple because of its unfeasibility to maintain. The analytical equipage developed in the last few years has made it possible to measure all kinds of chemicals (whether synthetic or natural) almost at the molecular level. In effect the Second Law of Thermodynamics defines the limits of food regulation within the context of modern-day analysis. The question whether the actual detection of some kind of molecule has any toxicological meaning has thereby come to the fore but has yet to be tackled openly. The history of CAP has shown that (food) safety on the one hand and (il)legality on the other hand is still confused in present-day regulation. The concept of hormesis could seriously ameliorate this situation simply because striving for absence of a certain chemical both from a regulatory and more importantly from a public health perspective is altogether unnecessary and even counterproductive.

Discussion and Conclusion

‘As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events.’ The EPA is quite clear on hormesis, and is not adaptive (yet) towards the advancement of scientific understanding in this field. We have interpreted this position as a misguided default safety approach; the widely used linear toxicological models serve as content for this approach. However, this default safety approach, which can certainly be typified as precautionary, will in generality fail because of the concept of hormesis.

The issue whether hormesis is a feature of organisms, whose response to a perturbation of homeostasis is hormetic in character is a matter of science, yet will have a profound impact on the risk paradigm of chemicals exposure and regulation. However, to keep questions of knowledge and power more or less separate in precautionary culture, will be hard to achieve. As an example, Axelrod et al. are very sceptical about hormesis and are of the opinion that scientific evidence does not support a universal extension of the concept to regulatory policy. Apart from the fact that scientific evidence does show thorough support of the concept of hormesis in terms of for instance endpoints, organisms, and chemical substances, their reference to powerful interests pressing for the incorporation of hormesis into regulatory policy is suggestive for their interrelated view on knowledge and power, and crucially weakens their argument against hormesis. Indeed, their opposition against the hormetic model derives predominantly from a worldview selection in science, (the justification-phase of science). Moreover, their comments are along the lines of green thinking as discussed above. Calabrese retorts succinctly:

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The horstic model is not an enemy to the public health community. Quite the contrary, it brings more information, strength, and options to the fields of toxicology and risk assessment. If properly used, it would enhance public health. The protectionist public health philosophy that guides current risk-assessment practices does not follow the data; rather, it follows an unscientific belief that only lower is better. It has become clear that this is not “universally” true and may be generally wrong and potentially wasteful of resources to improve the overall well-being of society.

My principal concern is that the attitude of fear that embodies the paper of Axelrod et al. has the potential to deny scientists their natural curiosity about this biological phenomenon and to see it only through political eyes. To do this will serve neither the scientific and biomedical communities nor the broader interests of society.

As scientific knowledge is increasingly linked to issues of power, the future of hormesis will be not so much a scientific matter, but a political (public matter), whereby the scientific issue of hormesis is reframed in a public context with its precautionary ‘green mentality’. This issue becomes an even bigger problem when a precautionary culture also is a culture of fear. It would, however, be vital to the EPA to not exclude hormesis upfront, as it would imply that state-of-art scientific knowledge and data as a matter of principle are excluded from assessment procedures when presumably it is not in line with the predominant worldview.

The only sensible approach, however, is to employ the best scientific insights of relevant risks and to adopt sensible assumptions in the face of inexorable uncertainty. Indeed, reference to the public debate—such as done by Axelrod et al., but also by Griffiths—in relation to the ostensible reluctance to accept hormesis, would weaken regulatory resolve to be sensitive to the best available strategies to protect public health. To decide what to do, regulators must go beyond the precautionary state of mind; it is useless and even incoherent for agencies to even attempt to be precautionary. Indeed, to be precautionary—as the global state of mind—begs the question: Precautionary in relation to what? Our contention is that the concept of hormesis needs to be further developed scientifically and unhindered in order to have its full implications for regulatory policy. Therefore the implications of hormesis are truly outside toxicology and pharmacology.

Trading off the consequences, costs and benefits, of a given action is an essential requirement of regulation, yet is currently hardly a matter of principle. The mere fact the precautionary principle is widely accepted especially in Europe is telling. The concept of hormesis shows that the search for safety is not a quest by means of linear extrapolation defaults, despite the EPAs preferences. The safety issue is complex; care about harm (or benefit) caused by exposure to a chemical compound implies care about the cost imposed by controlling the exposure. For instance, the failure of zero tolerance in food safety regulation for veterinary products without an MRL is the result of the unwillingness to review multiple sides of the regulatory equation. Precaution in food safety regulation was even still understood as the simple heuristic: ‘When in doubt, leave it out.’ For toxic substances, hormesis complicates the operation of the precautionary principle simply as stringent regulation might cause adverse health effects, rather than reducing them. This is important, as the target of food safety or chemicals regulation is life-saving potential (or health protecting potential).

Hormesis redefines our concept of ‘pollution’ and ‘contamination’. It questions the premise that ‘pollutants’ are unconditionally bad. This is innovative because modern environmental and public health legislation is built in large part on the moral dichotomies of good versus evil, clean versus dirty, natural versus unnatural. Chemical substances—be it natural or synthetic—are not either bad or good; they are both, depending on exposure levels and adaptive responses from the exposed organisms.

A first step towards regulatory development in light of the concept of hormesis would be to recognize that there are toxicological thresholds. As Cramer, Ford and Hall already remarked in 1978 in their seminal paper, which squarely at odds with the REACH: Safety evaluation is caught in a frustrating circle. It is neither possible nor sensible to try to obtain the information needed to assess every imaginable toxic risk associated with every substance, and pursuit of greater safety therefore demands the setting of priorities as well as sensible limits for investigation.

We therefore propose a TIE—a Toxicologically Insignificant Exposure level—for chemical substances. In light of analytical progress and its capabilities to detect minute amounts of chemical compounds a TIE would contextualise and rationalise the issue of chemicals exposure. Toxicity is obviously related to concentration—as it should be—and not to intrinsic characteristics of a certain target chemical compound, as to preclude analytical progress as a primary limiting factor for the determination of regulatory compliance. The concept of a TIE level goes beyond the moral ideal of ‘lower exposure is better’ and thereby challenges the current application of precautionary regulation. We believe it would add to cost-effectiveness of regulation, and could be a first step towards the incorporation of the concept of hormesis in regulatory policymaking.

We regard the TIE within the concept of hormesis, whereby insignificance is understood not as a regulatory evaluation based e.g. on a MTR (Maximum Tolerable Risk level) of 1:1 000 000, but is understood as a result of toxicological deliberation. Considering the hormetic U-shaped curve, beyond a certain point the moderate over-compensation as a result of the disruption of homeostasis re-establishes homeostasis, whereby the regulatory concern for toxicity no longer is required. The former approach is also known as the threshold of toxicological concern (TTC), which is a pragmatic risk assessment tool that is based on the principle of establishing a human exposure threshold value for all chemicals, below which there is a very low
probability of an appreciable risk to human health (defined in terms of the MTR). The TTC concept has been developed for chemicals exposure through food and expresses a de minimis concept acknowledging a human exposure threshold value for chemicals. Our contention is, as Cramer et al. remarked, that a TIE approach as well as for human as environmental exposure would increase cost-effectiveness of chemicals regulation as a first-step in incorporating the concept of hormesis.

REACH, as one of the most comprehensive initiatives in the field of chemicals regulation anywhere in the world, is the result of the old-school (linear) approach, and is in all intents and purposes unfeasible regarding economical and societal costs. Although basic economics will dictate the actual implementation format, the fundamental precautionary flaws will only surface when the reality of hormesis will be fully accepted and incorporated in the regulatory field. The EPA should not make this European mistake. The acceptance of hormesis would indeed be a paradigm shift –although the term seems to us overused- which, however, requires more than convincing colleagues in the field of toxicology and adjacent faculties. An effective paradigm shift also requires the public to understand and accept that chemicals exposure through different routes –such as food- need not be morally classified. However, the current regulatory witch hunt of synthetic chemicals, disguised as risk predictions of formalistically correct mathematical formulas devoid of biological meaning and ignorant of the health benefits of homeostatic exercise (which as the oxygen example shows, is an integral part of life itself) expresses the conservative moral of the cultural ecological critique that spawned precautionary culture. Unfortunately, the EPA, with its current rejection of hormesis as a viable model in the risk assessment procedure, takes the easy old-school route, which, as the European example of REACH shows, will take us further away from effective regulatory capabilities and will only address secondary risk management issues.

REFERENCES

7 Derived from Stenmark, note 3.
9 See note 3.
10 Appeal to authority (argumentum ad verecundiam): a proposition is held to be true because it is held by persons regarded to be authoritative in a specific field.
11 Appeal to consequences: the author points to the disagreeable consequences of holding a particular belief in order to show that this belief is false.
12 Appeal to force (argumentum ad baculum): the reader is told that unpleasant consequences will follow if they do not agree with the author.
13 Appeal to popularity (argumentum ad populum): a proposition is held to be true because it is widely held to be true or is held to be true by some sector of the population (e.g. upper class). This fallacy is sometimes also called the 'appeal to emotion' because emotional appeals often sway the population as a whole.
14 See for initial work on the sociology of knowledge: Fleck, L. Entstehung und Entwicklung einer wissen-schaftlichen Tatsache: Einführung in die Lehre vom Denkstil und Denkkollektiv. 1935, Benno Schwabe & C., Basel, Switzerland.
15 This rather unknown book has been given attention by Tomas Kuhn, who himself became famous for his work on the philosophy of science. Fleck's work is translated: Fleck, L. Genesis and Development of a Scientific Fact. 1979, The University of Chicago Press, Chicago.
16 See note 3.


Dahrendorf, R. *Class and Class Conflict in Industrial Society*. 1959, Stanford University Press.

See also Douglas and Wildavsky, note 17.


See also note 2.


See e.g. *Niet alle Risico’s zijn Gelijk*. Dutch Health Council, 1995, report 1995/06. [All risks are not equal]


See Stone, note 24.


See also note 2.


Rip formulates this issue in a bipolar fashion when he states:

‘Even without such explicit principles [referring to the precautionary principle; authors], there will always be trade-offs between overcaution and undercaution – in other words, which kind of error are we prepared to make?’

Förderinitiative Politik, Wissenschaft und Gesellschaft (Science Policy Studies), as managed by the Berlin-Brandenburgische Akademie der Wissenschaften.


38 See for the issue of precautionary choice in a cultural and historical perspective: note 2.


40 See note 21.


47 See note 46, p. 1.


49 See note 33.

50 Axelrod et al. for instance maintain on several grounds that hormesis is not the appropriate toxicological model to assess risks of chemicals exposure. However, their rejection of hormesis as a viable risk assessment tool is mainly based on the assumption that a public-health-protective approach is best served with the conservative classical toxicological approaches. Their disregard for the negative external costs as a result of the error of overregulation – for one - is typical for precautionary culture.

51 See e.g. on overregulation: Hanekamp, J.C.; Frappart, G.; Olieman, K. *Chloramphenicol, food safety and precautionary thinking in Europe. Environmental Liability*, 2003, 6, 209 – 221.


53 See for a thorough discussion of this issue: Bergkamp and Hanekamp, note 41.

See also note 34.


55 See note 54.


60 See note 11.


63 See note 58.

64 See note 54.

See also Calabrese, E.J.; Baldwin, L.A. *Chemotherapeutics and Hormesis. Critical Reviews in Toxicology, 2003, 33(3&4), 305 – 353. We are well aware of the essential-non-essential discussion in relation to chemicals exposure. Nevertheless, exposure to all kinds of chemicals—whether or not essential—has to be dealt with in a certain way by the exposed organism. Oxygen—an essential yet under certain conditions and concentrations toxic agent—shows that organisms have substantial adaptation capabilities.


76 See Bergkamp and Hanekamp, note 41.

77 REACH’s justification creates a contradiction: government failure calls in the view of the European Commission for more government action.


79 See Hanekamp, Verstegen, and Vera-Navas, note 2.

80 The European Chemical Bureau assessed the risk issues of phthalates rather differently (namely absent): *European Union Risk Assessment Report, 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-“isononyl” phthalate (DINP). 2003, Volume 35, EUR 20784EN.

81 See note 50 and note 2.

82 See note 51.

83 See note 75.

84 See note 23.


87 See note 39.

88 See note 54.

89 See note 50 and note 2.


91 IPCS-INCHEM (Chemical Safety Information from Intergovernmental Organizations), webpage http://www.inchem.org/documents/jecfa/jecmono/v33je03.htm (last visited on the 3rd of January 2006).

92 IPCS-INCHEM (Chemical Safety Information from Intergovernmental Organisations), webpage http://www.inchem.org/documents/jecfa/jecmono/v33je03.htm (last visited on the 3rd of January 2006).


95 Policies aimed at the exclusion of risk or that generate an impossi-
‘130. Supported more specifically by Fedesa and Fefana, Pfizer submits that in any such risk assessment, the Community institutions must show that the risk, although it has not actually become a reality, is nevertheless probable. The existence of a ‘very remote risk’ should be allowed given the concrete positive elements arising from the use of the product concerned. In any event, the Community institutions cannot legitimately apply a test which Pfizer describes as a ‘zero risk test. Such a test is inappropriate since it is impossible to satisfy. It amounts essentially to requiring proboatio diabolica from the industry, something which is recognised as unlawful in all the legal systems of the Member States (Opinion of Advocate General Mischo in the Greenpeace case cited at paragraph 115 above, ECR I-1651, at I-1653, point 72). It is never possible to prove conclusively that a chemical or pharmaceutical compound or anything created by modern technology represents a zero risk to public health now or that it will do so in the future. To apply such a test would quickly lead to the paralysis of technological development and innovation.’

See also: Keeney, R. Understanding Life-Threatening Risks. Risk Analysis, 1995, 15(6), 627 – 637.

97 See note 34.

99 See note 50.
102 See note 21.

104 See note 34.


111 See e.g.: Calabrese, E.J.; Cook, R.R. Hormesis: how it could affect the risk assessment process. Human & Experimental Toxicology, 2005, 24, 265 – 270.

112 See Rozman and Doul, note 57.
COMMENTARY: PRECAUTIONARY PRINCIPLE FOR TOXIC CHEMICALS – NO ALTERNATIVE TO SAFEGUARD SOCIETAL BENEFITS

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Precautionary measures are increasingly (mis)used by regulators and politicians to ban or limit the use of substances – either through legislation or substitution pressure – despite the existence of meaningful and robust results of the official risk assessment process. A substantiated state of knowledge and broadly accepted opinion is therefore badly needed to objectify the discussion and to obtain acceptance for a practicable guidance which can be basically derived from the Art. 15 of the Rio Declaration (1992).

J. Hanekamp et.al.¹ have copiously elucidated in their article the ambiguity of social behaviour in developing an increasing risk-adversity but accepting the “safer human life in modern society” as being a risk-free by-product of industrial activities. They laid stress on the point that society basically accepts the mere presence of a man-made chemical substance being a risk per se whilst ignoring the facts that there is often a benefit even at small doses. This public perception on precautionary action is a contradiction in itself as the achievements of the past industrial developments without which the societal safeguarding of a longer, healthier and more comfortable life would have been never possible is based on the acceptance of certain risks. Risk management is part of our daily life and each individual is evaluating risks and appropriate management measures itself when it passes a highly frequented street, smokes a cigarette or enters an airplane. What makes the difference between personal risk management reflecting the sanctity principle and the political call for the precautionary principle?

There is of course no easy answer. By thoroughly analyzing the precautionary principle as integral part of the toxic-free regulatory approach of the US based Environmental Protection Agency (EPA) and the European Commission Hanekamp highlights the arbitrary risk selection approach with specific emphasis on the new EU chemical regulation called REACH. As this new regulation is basically focusing on synthetic chemicals it intrinsically underpins the perception that man-made substances are contributing to an intoxication of human beings in general. The most important misconception in this particular regulatory approach is based on the fact, that the risk perception is directly proportionate to the physico-chemical and toxicological properties of the substance itself. It does not really consider the combinatory effect of exposure to a substance and its properties being the risk factor for human life or the environment. In the contrary, many substances are under suspicion due to their hazardous profile like persistency or bio-accumulative potential which might be an intended property of the substance to guarantee a distinct application profile. It needs to be mentioned of course that where hazards and risks are known it is always a question of proper and effective risk management ensuring that exposure is controlled in a reasonable way. The foreseen consequence under REACH would be to subsequently eliminate such substances by substitutes. Would it then be an appropriate solution to substitute a man-made substance by a natural substance with the same chemical or toxicological performance knowing that in virtually all cases synthetic and natural chemicals have common modes of action? Obviously not, because it would at least fall under the scope of REACH as soon as it has to be classified as dangerous substance even though not chemically modified.

It is, however, worth mentioning that over 99 per cent of the chemicals we’re exposed to day-by-day are of natural origin. Many of them are toxic or even carcinogen as well but they are not perceived as being dangerous due to their “green” image. These toxins are normally produced within the plants as intrinsic protection mechanisms against outside enemies like fungi, insects or vertebrates. As the nature is challenging the human health all the time with chemical attacks it seems to be a paradox that internal repair mechanisms like DNA repair or cellular defence mechanisms of the human body as such will be switched off as soon as man-made chemicals enter the body whilst functioning properly in all other cases. J. Timbrell ² has recently published his book titled “The Poison Paradox” which is tackling the chemical hysteria and describing the ambiguity of chemicals being friends and as well foes.

What defines a real risk to human health or the environment? Following the approach of various environmental campaigners it would be the sole presence of a chemical in the blood or the breast milk verified in amounts close to the detection limit which determines the risk. These groups are deliberately mixing risk with hazard thus trying to emotionalize the discussion about regulatory requirements for safe chemicals management and to force politicians to take decisions based on flawed or false information. The achievements of state of art analytical methodologies and procedures which is nowadays capable to detect trace amounts of substances in highly complex
matrices will become the gravedigger of modern chemistry. New chemicals designed to serve as effective drugs, industrial intermediates or highly functional additives in various applications will be detected next in body liquids or tissues due to their vapor pressure and related molecular presence in the breathing air, water or direct contact material. Even if these chemicals will be intensively tested before they enter the market many questions especially those related to toxicological or eco-toxicological implications in complex interactions may not/ can not be answered immediately. The chemical industry is taking its product stewardship program very seriously and recognizes the need for more data to ensure proper management of substances, but even extensive testing of substances will not take the society to zero risk which basically should place more confidence in hormesis becoming the default position for low dose effects. Precautionary actions, misinterpreted by environmental pressure groups will mislead policy makers and undermine innovative developments urgently needed to help solving the next generation’s problems like safe nutrition, drinking water or sufficient medication.

In this context it should be noted that Britain’s leading toxicologists recently publicly condemned the “hysterical, scaremongering” approach of pressure groups. The following quotes of A. Boobis, Imperial College London (Sept. 2005):

(Many chemicals) “can cause diseases but not at the levels found in these test … Most chemicals were found at a fraction of a part per billion. There is no evidence such concentrations pose any threat to people’s health”

and K. Donaldson, Edinburgh University (Sept. 2005):

“We do not say these chemicals are completely safe but that there is no evidence – so far – to show tiny traces are unsafe”.

basically support the conclusion of the Centers for Disease Control and Prevention (CDC) in its 3rd national report emphasizing “just because people have an environmental chemical in their blood or urine does not mean that the chemical causes disease.”

In contrast to this more negative impression of chemicals being not harmful in lower concentrations it is well known that well established toxins can even have beneficial and therapeutic properties at low doses. J. Hanekamp refers to this positive horismic effects of potentially toxic chemicals in his article and puts it into context with REACH. Given the fact, that the phenomenon of hormesis is gaining more and more scientific support and is, as E.J. Calabrese pointed out recently, based on a sound data base of nearly 6000 examples, it did not find its way into the public policy yet. The “old fashioned” way of evaluating the risk of a toxic chemical would have to be changed dramatically and this actually is in blatant contradiction to the approach taken by the European parliament and Council in its adoption of the precautionary principle and substitution approach for CMRs, PBTs and vPvBs in the broader context of REACH. Hormesis does and should have the potential to substantially stimulate a change in the policy for regulating toxic chemicals in future.

There are, of course, emotional aspects to be carefully considered by politicians and it can be really difficult to spot the real issues when there is controversial discussion about toxicological aspects of especially carcinogenic substances at low doses. Absolute reassurance and “no risk” policy is, however, contributing to the risk adversity of our society and triggers biased regulation which will not deliver substantial environmental or health benefits.

The typical human response to risk is asymmetrical: in general, action to avoid a loss will be prioritised over action to achieve an equally probable gain of the same size. "Precaution" may thus be seen as a natural human response to such risks, and is the default in societies which lack risk-apportioning institutions.

Over the course of the past two thousand years, most human societies have developed institutions that enable them to reduce their exposure to, or to mitigate involuntary risk. Particularly important have been property rights, civil liability, contracts, and the rule of law. Administrative controls, including specific health, safety and environmental regulations, have also been introduced in order to reduce both voluntary and involuntary exposure to risk. Meanwhile, science, which has developed in parallel, has provided the basis in many cases for improvements in our ability to address risks in general.

In combination, these have enabled us to overcome our innate precaution and engage in potentially beneficial risk-taking activities. As a result, new products and processes have been developed that have improved human lives in myriad ways. In the past two centuries, increases in per capita production of food, improvements in the availability of clean water and sanitation, and innovations in vaccines and medicines have contributed to substantial reductions in infant and child mortality, as well as mortality and morbidity from a wide range of ailments. More generally, the increase in productivity occasioned by the development of new processes of production has led to substantial increases in wealth, better enabling billions of people to pursue their goals.

Paradoxically, increases in wealth and the reduction in involuntary exposure to real risks, such as malnutrition, coliform bacteria, and black soot have made people more susceptible to less important and even hypothetical threats. In large part this can be explained by the aforementioned asymmetrical response to risk.

To compound this, the past thirty years have seen a series of regulatory failures, in particular the BSE fiasco in the UK, the toxic chickens and beverage scares in Belgium, and the scare over human sewage used as animal feed in France, which have contributed to a weakening of the public’s trust in the regulatory state. In addition, these scares as well as various examples of apparent and real corporate malfeasance, such as the Bhopal disaster in India and the Seveso incident in Italy, have undermined public trust in corporations. Moreover, these events have heightened the perception that modern technologies present untold hazards and sensitize us to claims of future possible risks.

Activist organisations and the media rationally play to this combination of an innate precautionary risk response and our recent sensitization to possible threats. Environmentalists and consumer activists highlight hypothetical threats in order to induce us to contribute to their cause. They then use the money they raise to support campaigns the objective of which is to increase their own power and influence. An example is the promotion of ideas such as the ‘precautionary principle’ (PP), which they have pushed in many ways not least through sponsoring lawyers to write articles claiming that the PP is a principle of customary international law.

Journalists write sensational stories about these threats in order to induce us to watch, listen or read their stories – and so contribute to revenue raised through advertisements (many of which are from the aforementioned discredited corporations) and sales to the public. The public, meanwhile, is presumably attracted to ‘bad’ news for the same reason that we have an innate precautionary response: our ancestors needed to take seriously and acquire information on possible major down-side threats, such as the imminent arrival of a large carnivore. The opportunity cost of acquiring and processing relevant information (not to mention the difficulty of comprehension for many) means that most members of the public remain rationally ignorant of the underlying science pertaining to these hypothetical threats. The result is clearly observable: So long as the hypothetical risks cannot be dismissed entirely, the public is led to believe that a precautionary response is necessary.

Companies – who need the public to trust their products – have responded by increasing their vigilance and by offering specialist products that meet the perceived demands of threat-sensitized consumers. Retailers in the UK now offer to their middle-class consumers a wide range of ‘organic’ products, a class of goods whose dominant characteristic seems to be the small number of synthetic chemicals permitted for use in their production. So far this gone that even some mineral water brands now advertise that they are filtered through “organic” soil.
Governments have addressed some of the causes of the regulatory failure. In the UK, for example, the Ministry of Agriculture, with its dual and often conflicting role of promoter and regulator of agriculture, was abolished and two separate bodies – the Department for Environment Food and Rural Affairs and the Food Standards Agency – were established. One consequence of this has been possible over-regulation across the EU. A good example is the recent withdrawal of food products containing two red dyes (Sudan 1 and Para Red). These are rodent carcinogens, but in the amounts consumed by humans in food, were unlikely to be harmful; depending on their human dose-response curves, they might even be hormetic. The withdrawals cost tens, possibly hundreds of millions of pounds – to little if any benefit in terms of human health: it is doubtful that even one life was saved as a result.

Hanekamp and Bast (H&B) offer an interesting and in many ways plausible explanation of the relationship between science, society and the regulatory state. They then consider the implications of an increasingly ‘precaution’ dominated society both for regulations and for society itself.

They argue quite convincingly that the failure on the part of regulators in both Europe and the US to utilise hormetic models in toxicological studies is at least in part explained by the misguided obsession with precaution and that the “precautionary ‘green mentality’” of the public may prevent adoption of hormesis as the basis for regulation.

I had some quibbles with H&B’s analysis. Why for example should the fact that “Research efforts usually require large sums of money” result in “the mandatory involvement of government”? This is of more than prosaic interest because, as H&B observe, when government funds science, “people in power often decide the kind of research that ‘should’ be initiated.” Terence Kealey has shown that government funding of scientific research mainly crowns out the private sector, whose incentives are better attuned to delivering results; he notes in particular that all the scientific advances that took place during the agricultural and industrial revolutions were the result of private endeavours. Reduced government funding of science would lead to a greater diversity of interests driving research and should be expected to reduce the capacity for incumbents to hinder research into and adoption (for regulatory and other purposes) of competing theories.

In addition, I wonder if H&B exaggerate the extent to which we live in a precautionary culture, as opposed to a culture that has been excessively sensitized to specific threats. As Cass Sunstein observes “Simply as a logical matter, societies, like individuals, cannot be highly precautionary with respect to all risks. Each society and each person must select certain risks for special attention.” Sunstein goes on to offer a plausible explanation as to which risks become the subject of precautionary regulation based on what he calls the ‘availability heuristic’: “Sometimes a certain risk, said to call for precautions, is cognitively available, whereas other risks, including those associated with regulation itself, are not. In many cases where the Precautionary Principle seems to offer guidance, the reason is that some of the relevant risks are available while others are barely visible.”

Notwithstanding these criticisms, H&B’s proposal of an alternative to current methods for setting exposure limits – the ‘toxicologically insignificant exposure’ level – seems eminently reasonable. Let’s hope that the EPA takes note. If it does – and the regulatory toxicology paradigm is thus suitably shifted – perhaps the EU institutions will be forced to wake up to the folly of their over-reaching regulations.

1 Executive Director, International Policy Network, London; Visiting Professor, University of Buckingham Department of International Studies.
6 Ibid.
7 John Adams argues that we have an innate ‘risk thermostat’ and that as one risk is removed, so we seek out others. Adams, J. Risk. 1995 UCL Press
10 BBC. France Warned over Animal Fred. 1999, October 23. Available at: http://news.bbc.co.uk/1/hi/uk/482625.stm
14 The Sudan 1 die was present at concentrations of 3mg/kg in Worcester sauce and 80mg/kg in chilli – see Commission Memo (MEMO/05/67), 2005, 25 February, available at http://www.foodlaw.rdg.ac.uk/news/eu-05015.htm — yet rodent tests show no carcinogenic impact when Sudan 1 was fed to rats in quantities of 30mg/kg of body mass, according to Imperial College toxicologist Prof. Alan Boobis – see: Derbyshire, D. Contradiction, Hype and a Question of Risk, Daily Telegraph, 2005, 23 February. To achieve
body mass levels of even 3mg/kg in humans would require the con-
sumption of more chilli and/or worcester sauce than is imaginable.
Perhaps unsurprisingly, the EU Commission report used much
higher levels (250 mg/kg and 500 mg/kg in rats; 500 mg/kg and
1000mg/kg in mice) in order to justify its assertion that Sudan 1 is
carcinogenic and genotoxic – see: The EFSA Journal. 2005 263, 1-
71.
15 Christine Seib. Premier Foods faces £100m bill for Sudan 1. The
Times, 2005, February 26. Available at: http://business.timeson-
line.co.uk/article/0,,9065-1501124,00.html
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Chicago Law School: John M. Olin Law and Economics Working
Paper No. 20. at 13.
18 Ibid. at 16.
COMMENTARY ON HORMESIS AND PRECAUTION: THE TWAIN SHALL MEET

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Abstract

Regulatory focus on quantifying risk of disease or death from exposure to hazardous substances via monotonic dose-response models has either downplayed or even rejected potential benefits to human health from exposures to low (sub-threshold) doses, represented by either U-shaped or J-shaped models. Thus, most environmental health policy hypothesizes, without firm evidence, that cancer risk is proportional to exposure at low doses of current and routine ambient exposures. An acceptable exposure is determined by either setting a somewhat arbitrary “acceptable” level of risk, such as one in a million excess individual lifetime cancer risk or, in the case of several types of animal toxicological test results, applying multiplicative safety factors to a specific concentration, generally derived from a benchmark dose or NOAEL. This seemingly precautionary approach is questionable in light of much experimental evidence indicating protective effects of exposure at low doses — U-shaped or J-shaped models. We demonstrate that incorporating the possibility of hormesis into regulatory decision-making is precautionary, while use of defaults results in policy conflicts with precaution.

Introduction

Hanekamp and Bast (this issue of BELLE, 2006) raise the question of whether the regulatory process should explicitly include biphasic dose-response models that characterize “hormesis” in the portfolio of routinely used dose-response models. They consider the fact that models of dose-response based on default hypotheses, such as the linear no threshold dose-response functions (or models), or on the interpolation to zero from a confidence limit, are certainly less accurate than J- or U-shaped empirical (and thus demonstrable at the sample, and often theoretical inferential levels) relationships.

Unfortunately, unproven conjectures and default assumptions too often trump facts in science-policy. The reasons arise from a complex mix of historical bias, regulatory conservatism and inertia, deference by the judicial to the regulatory agencies that cause a failure in the critical examination of scientific pronouncements by an agency, and other factors. Inflated statistical extrapolations of diseases or deaths averted; the cost of regulatory compliance; the time needed for a regulation or guideline to be implemented, take hold and “show” results; the effects of diverting funds should the results of implementation not be consistent with the truth; and the increases in diseases or deaths actually caused if the causal association conjectured by the regulators is incorrect have all contributed to a murky science-policy instead of a system of inclusion that would benefit society economically and with improved public health.

As Calabrese (2005) has remarked, historically:

“... the research of numerous experimentally oriented scientists during the late 19th and 20th centuries ... revealed that the nature of the dose-response was sigmoidal (i.e., S-shaped) with a marked increase in response between approximately 20-80%, while asymptotically approaching 0 or 100% in the tails of the distribution. This made the estimation of the 50th percentile ... quite reliable, while estimations of < 1 or > 99% highly uncertain ...”.

The policy and health implications of such S-shaped (sigmoid) models are that:

“The sigmoidal dose-response led to the belief that thresholds exist at low doses. Numerous observations suggested that as the dose was progressively decreased the response became more like the control value, regressing into the ‘noise zone’ of the controls and becoming indistinguishable from it.” (Ibid)

On this basis, beneficial effects from any exposure are not accounted for; hypothesized adverse effects are reduced to an “acceptable” or “tolerable” level. The presumption is that exposures or doses lower than the threshold dose do not create effects large enough to require consideration. This apparent neutrality is achieved at the potential social cost of denying beneficial effects. But, of course, this is no neutral result: reaching supposedly protective science-policy goals is expensive and generally incommensurate with most public expenditures incurred in developing healthy or safe conditions for those at risk.

Discussion

The early bio-statistical aspects of the sigmoid dose-response model were studied using the probit transformation (of the probability of response given dose or concentration). In the 1930s, this allowed estimates of threshold values via statistical methods, which account for the uncertainty in the estimation via the upper and lower confidence limits of the probit line. The importance of this empirical form of analysis is that — in principle and often in practice:

1. it set up a testing protocol in which doses higher than the controls were needed for estimation,
2. it much simplified the statistical analysis (the probit transformation resulted in a linearized model rather than a non-liner model; the S-shaped function itself is of course monotonic and non linear) which, in those days required complicated methods,
3. it imposed a factual bias in the experimental protocol by limiting each study to results above the con-
The exception to the prevailing line of reasoning represented by the S-shaped dose-response was the carcinogenic dose-response model, which began with the impact of ionizing radiation on somatic mutations, resulting in the proportionality assumption at low dose (commonly referred to as the single-hit theory of carcinogenesis, later mechanistically improved by the multistage model, which is still linear at sufficiently low doses). These initial approaches were either deterministic, solving differential equations involving the change in the number of cells over time, or stochastic. Concepts of tolerable dose of ionizing radiation were based on skin erythema (Mutscheller, A., Physical Standards for Protection Against Roentgen Ray Dangers, Am. J. Roentgenology (1925), 13:65-69), but not on mutagenic or cancer effects of that radiation. This concept has lead to regulatory cancer models such as the single-hit and multistage models and the concept of “acceptable risk,” found in US environmental and safety laws.

More recently, the linearized multistage cancer dose-response model (LMS), which is used by the US EPA and the US FDA for developing potency factors (measured by the slope of the linear portion of these dose-response models, under the assumption of lifetime exposure), is based on constraining the parameters of the LMS model (the workhorse of the US EPA regulatory work on cancer) to be non-negative ($\geq 0$) and using the linear portion of the model for regulatory purposes. This artificial constraint prevents the finding of a threshold, when it exists, or the potential for a beneficial effect from very low levels of exposure, when they exist. Moreover, the US EPA’s LMS formulation is an approximate solution rather than an exact one. The exact solution, which should be used instead of the approximate solution, is less restrictive (Cox, LA, Jr, Exact Analysis of the Multistage Model Explaining Dose-response Concavity, Risk Analysis, 15:359-368, 2005).

Calabrese (2005) has commented that:

“… the normal process of ‘peer review’ with respect to … hormesis … became ‘institutionally affected by … historical ‘toxicological correctness’ that was an outgrowth of the prolonged antipathies between traditional medicine and homeopathy. Moreover, this failure was far greater than the occasional irregularities in the … peer review … but a more insidious phenomenon occurring at multiple levels (e.g., academic, governmental, professional … ) affecting the most central aspect of toxicology (i.e., the nature of the dose-response) over several generations of pharmacologists/toxicologists.”

We do not wish to engage in this debate nor in the historical genesis of the S-shaped model, which has been described by Calabrese (2005) and traced to the U.K.’s medical influence on quantitative toxicological reasoning. Rather, we take a more limited aspect of causal reasoning. Beliefs can be unwittingly biased by past experience. Therefore, experimental studies that are repeated in many places and with different test systems (e.g., rats, mice, and so on) can overcome some of the biases that are created in attempting to develop causal models. Unfortunately, if a particular belief based on empirical fact is held by many, then the few who argue for a contrary belief will not necessarily be heard. It is the facts that are questionable, not the beliefs. That is, if the experiments are constructed to test responses in the controls (unexposed to the substance of concern, but nonetheless possibly responding with the adverse outcome) versus groups that are exposed and that respond with rates that are greater than the control, then it is natural to think of an empirical s-shaped dose-response.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>$\delta$-Limonene</th>
<th>Mercuric chloride</th>
<th>Phenylarsine</th>
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<tbody>
<tr>
<td>Arsenate</td>
<td>Diacetotescipenol</td>
<td>Mercuric nitrate</td>
<td>Selenium</td>
</tr>
<tr>
<td>Arsenite</td>
<td>Diesel exhaust particle</td>
<td>Methoxacetic acid (metabolite of 2-methoxyethanol)</td>
<td>Silver nitrate</td>
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<tr>
<td>Asbestos</td>
<td>1,1-Dimethylhydrazine</td>
<td>Methyl mercury</td>
<td>Sodium azide</td>
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<tr>
<td>Azide</td>
<td>Dioxane</td>
<td>Methyl nitrosourea</td>
<td>T-2 toxin</td>
</tr>
<tr>
<td>Cadmium chloride</td>
<td>Ethyl carbamate</td>
<td>$N$-methyl-$N$-nitro-$N$-nitrosoguanidine</td>
<td>TCDD</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>EMF (electromagnetic frequencies)</td>
<td>Nickel</td>
<td>Tributyltin</td>
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<tr>
<td>Chloretolbinol</td>
<td>Formaldehyde</td>
<td>Paraquat</td>
<td>Trichothecenes (Isosaturoxin, Rotrodin A, Saratotoxin G, Saratotoxin H, Verrucarin)</td>
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<tr>
<td>Chromium (K,Cr,O,)</td>
<td>Hexachlorocyclohexane (a-isomer)</td>
<td>PBB</td>
<td>Trichlorophosphate</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Hydroquinone (metabolite of benzene)</td>
<td>PCB</td>
<td>Vanadium (sodium metaranadate)</td>
</tr>
<tr>
<td>Copper sulfate</td>
<td>Lead</td>
<td>Pesticide mixture (atrazine, metribuzine, endosulfan, lindane, aldicarb, and dieldrin)</td>
<td>X-ray</td>
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<td>Copper(2) acetate(4)</td>
<td>Mercuric acetate</td>
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<td>Zinc chloride</td>
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Table 1. Toxic substances inducing immune-system-related hormetic-like biphasic immune responses (Calabrese and Baldwin, 2003a).
A large number of substances have demonstrated hormetic immune responses, and this number continues to grow as more research is conducted. In 2003, Calabrese and Baldwin, reported forty-eight such substances (Table 1). In addition, these responses have been found in numerous different animal species (Calabrese and Baldwin, 2003a), which indicates that this behavior is not specific to a certain lab animal and most likely extends to humans. With such widespread evidence, it is essential to the precautionary principle that hormetic dose-response be considered in regulations.

**Policy Implications**

The US EPA (2004) states that:

> Because of data gaps, as well as uncertainty and variability in the available data, risk cannot be known or calculated with absolute certainty. Further, as Hill (1965) noted, a lack of certainty or perfect evidence 'does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.'

This US EPA statement supports a regulatory process that must account for hormetic response, when that type of response is demonstrated through sufficient experimental and mechanistic knowledge. Specifically, a policy can include affirmative action as well as no action. In these polar situations, subsequent learning (and updating via Bayesian or other updating rules) may or may not change the direction of the initial choice. In particular, if hormetic behavior has been demonstrated, but sub-threshold protection via safety factors applied to the NOAEL has not, it seems that policy must confront, explain, and resolve this asymmetry. The negation of demonstrable benefits while basing policy on an indemonstrable possibility may result in incorrect and possibly dangerous outcomes for society. This point becomes even more evident when we consider a special form of selection bias. Namely, only citing the supportive literature and either ignoring or giving short shrift to opposing views that can be the result of many consensus-based opinions.

Another issue that also has serious implication for the search for causation is the failure of peer review. As a most recent case, consider cloning and retractions: this, and several other prominent cases, exemplify that the peer review process is not as fail-safe or rigorous as is desired. It is also troublesome that the original data are often not provided to reconstruct the analyses that have appeared in peer-reviewed journals. Finally, it is often unclear how accurate the peer review process can be.

**Review of Scientific Evidence**

The issue of peer review and acceptable scientific evidence has forced judges to explicate how scientific evidence will be used. *Chemical Manufacturers Association v. EPA*, details the issues for judicial review. These include: the amount of the releases (being substantial), exposure being substantial or significant and a rational connection between the facts ... and the choices but the agency need not rely on quantitative risks and benefits. The more likely than not standard is understood as being approximately equal to 51% in favor of a proposition. This means that the relative risk (RR) should be greater than 2.0 and statistically significant to meet this (legal) standard. For example, the US Supreme Court, in *Industrial Union*, held that the agency had the burden of showing that it is at least more likely than not that long-term exposure to 10 ppm of benzene presents a significant (a qualifier that does not appear in the statute) risk of material health impairment. In this case, the Court required OSHA to develop better evidence of adverse effects (leukemia) from occupational exposure to airborne benzene, and concluded that safe is not equivalent to risk-free. The significance of risk is not a mathematical straitjacket and OSHA's findings of risk need not approach anything like scientific certainty. As the Court stated:

> “The reviewing court must take into account contradictory evidence in the record..., but the possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's findings from being supported by substantial evidence.”

Importantly, the Court refused to determine the precise value of significant risk. Although it noted that chlorinated water at one part per billion concentrations would not be significant, but one per thousand risk of death from inhaling gasoline vapor would be, it did not provide the value of the risk acceptance (or tolerability) criterion. The absolute risk-based standard is zero risk, which is neither an empirically demonstrable or even useful requirement.

In 2002, the US Office of Management and Budget, OMB, concluded that precaution plays an important role in risk assessment and risk management, but precaution, coupled with objective scientific analysis, needs to be applied wisely on a case-by-case basis (US EPA, 2004). Following the 1991 Executive Office of the President document Regulatory Program of the United States Government (US EPA, 2004), risk assessment has specific requisites:

> “a) Risk assessments should not continue an unwarranted reliance on ‘conservative (worst-case) assumptions’ that distort the outcomes of the risk assessment, ‘yielding estimates that may overstate likely risks by several orders of magnitude.’

> b) Risk assessments should ‘acknowledge the presence of considerable uncertainty’ and present the extent to which conservative assumptions may overstate likely risks.

> c) EPA risk assessments must not ‘intermingle important policy judgments within the scientific assessment of risk.’ Rather, the ‘choice of an appropriate margin of safety should remain the province of responsible risk-management officials, and should not be preempted through biased risk assessments.’”

**Information Quality**

The US Office of Management and Budget (OMB) has established a set of Final Guidelines, the *Information Quality Guidelines* that controls all US federal agencies regarding the collection, processing and dissemination of information that has to do with risk assessment. The Guidelines apply to scientific information used by federal agencies. Specifically, the OMB refers to the Safe Drinking Water Act as the gold standard for justifying public decision-making based on risk. The SDWA applies to what the OMB calls influential information, as follows:

> “(A) Use of science in decision-making. In carrying out this section, and, to the degree that an Agency action is based on science, the Administrator shall use:

> i) the best available, peer reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and...”

26 BELLE Newsletter
The estimates of carcinogenic risk of death due to radon from exposure to radon in which:

(i) each population addressed by any estimate of public health effects;
(ii) the expected risk or central estimate of risk for the specific populations;
(iii) each appropriate upper-bound or lower-bound estimate of risk;
(iv) each significant uncertainty identified in the process of the assessment of public health effects and studies that would assist in resolving the uncertainty; and
(v) peer-reviewed studies known to the Administrator to support, are directly relevant to, or fail to support any estimate of public health effects and the methodology used to reconcile inconsistencies in the scientific data.”

Influential information is defined to be that scientific, financial, or statistical information, which will have or does have a clear and substantial impact on important public policies or important private sector decisions. Some US Federal agencies have adapted the SDWA guidelines for influential information. For example, the Centers for Disease Control and Disease Prevention, CDC, had adapted the OMB Guidelines (CDC can legally do so) to deal with judgments based on qualitative information as follows:

1. The best available science and supporting studies conducted in accordance with sound and objective practices, including peer-reviewed studies,
2. Data collected by accepted methods (if reliability of the method and the nature of the decision justify use of the data),
3. Ensure that information disseminated to the public related to risk effects is comprehensive, informative and understandable.

The OMB Guidelines also allow an individual to bring civil law suits to challenge the value of the influential information, including risk assessments.

Judicial Review of Regulation

The traditional rule in US administrative law makes the proponent of the rule bear the burden of proof; but the evidentiary standards are less demanding than in tort law. In general, judicial review of agency actions is based on the liberal notion (i.e., giving much latitude to an agency) called the arbitrary and capricious test. However, federal courts can review the record, including the scientific evidence, under the hard look theory. Determining whether the agency’s decision is supported by substantial evidence requires finding that the administrative record contain(s) respectable scientific authority supporting the agency’s factual determinations. Under the hard look, agency rulemaking will be sustained if: i) there is a reasoned explanation of the basis of fact, ii) its decision is supported by substantial evidence, iii) other alternatives were explored, and given reason for their rejection, and iv) the agency responded to public comments. For instance, medical evidence of exposure to lead and resulting anemia, and other adverse effects on the red blood cells and neurological effects led the court to find that the US EPA had not acted unreasonably when the uncertainty of the adverse effects was large. The hard look has been used to ascertain the validity of an agency’s choice of mathematical models, challenging the technical assumptions made by another agency and requiring documentation of the health effects of 428 toxic substances.

The opposite of the hard look is the soft glance in which:

“because substantive review of mathematical and scientific evidence by technically illiterate judges is dangerously unreliable, I continue to believe that we will do more to improve administrative decision-making by concentrating our efforts on strengthening administrative procedure.”

(Judge Bazelon, in Ehrhl Co. v. US Environmental Protection Agency).

American courts are often deferential towards rules and regulations issued by public agencies. For instance, in Chevron v. Natural Resources Defense Fund, involving the interpretation of a Section of the Clean Air Act, the Court stated that:

“the Administrator’s interpretation represents a reasonable accommodation of manifestly competing interests and is entitled to deference: the regulatory scheme is technical and complex, the agency considered that matter in detailed and reasoned fashion, and the decision involves reconciling conflicting policies... Judges are not expert in the field, and are not part of either political branch of the Government... When a challenge to an agency construction of a statutory provision, fairly conceptualized, really centers on the wisdom of the agency’s policy, rather than whether it is a reasonable choice within a gap left open by Congress, the challenge must fail.”

Deference can result in a judicial unwillingness to deal with uncertainty. For instance, the US Nuclear Regulatory Commission was held to be free to adopt conservative assumptions by risking error on the side of over-protection rather than under-protection... when those assumptions have scientific credibility. The estimates of carcinogenic risk of death due to radon from uncontrolled uranium mine tailings, was calculated by the Commission to be one in fifty million, compared to the background cancer risk of death from ionizing radiation, which is approximately fifty per million. However, for residents near a uranium mine with uncontrolled tailings, the radon-related risk had been calculated to be one in two-thousand six-hundred person-lifetimes exposure. This result was a satisfactory basis for finding an unreasonable public health risk: unreasonable risk (15 USC §2058(f)(3)(A)) is a quantitative measure of excess risk over background. The court accepted the Commission’s bounding of that risk somehow between one in two thousands and one in fifty million, is appropriately left to the Commission’s discretion, so long as it was reasonable. Deference to agency rulemaking is well established.
The policy question inherent to our arguments is not whether any particular environmental health policy is sound or not; the answers require legislative and legal analyses that have been developed elsewhere (Ricci and Straja 2005). Rather, the question is whether a scientifically sufficient set of theoretical and empirical results has been achieved such that regulatory science-policy is compelled to account for them, rather than – by policy fiat – not do so. Our question is motivated the asymmetry between facts and conjectures found in US EPA (2004):

"As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events (U.S. Environmental Protection Agency, An Examination of EPA Risk Assessment Principles and Practices, 2004, EPA/100/B-04/001)."

This form of US EPA’s policy, discussed in Hanekamp and Bast (2006) in this issue of Belle, is a much less formal statement of Toby Page’s (cited in Henekamp and Bast) earlier policy argument that:

“When a regulator makes a decision under uncertainty (in reality, under risk, not uncertainty, Ricci, 2005) there are two possible types of error. The regulator can (either) overregulate a risk [false positive, author] that turns out to be insignificant or … can underregulate a risk that turns out to be significant. If the regulator erroneously under-regulates [false negative, author], the burden of this mistake falls on those individuals who are injured or killed, and their families. If a regulator erroneously overregulates, the burden of this mistake falls on the regulated industry, which will pay for regulation that is not needed. This result, however, is fairer than setting the burden of uncertainty about a risk on potential victims.”

Although there are many other types of statistical error well beyond these two basic errors (which are inherent to the classical tests of the null and alternative hypotheses) in dealing with causal constructs (Ricci, Cox and MacDonald 2004a,b 2005), we can formalize their argument by including:

**Scientific conjectures.** These arise when causal models are unknown.

**System (model) misspecification.** An example might be the exclusion of fundamental variables in a multi-component model. Specification often refers to the choice of mathematical form (linear, polynomial, and so on) and the variables excluded: relevant explanatory variables that cannot be accounted for by random error. For example, a choice of dose should account for biochemical changes that occur after exposure as the chemical moves through physiological and biochemical pathways to reach the target organ.

**Statistical uncertainty.** This is a familiar form of uncertainty that generally refers to the natural variability of data (e.g., sampling variability).

A determination of the burden of the disease or death from environmental or occupational exposures is strictly a scientific matter; an allocation of the costs to reduce or eliminate such burden is a...
matter of policy, which is the result of consideration of equity, assumption of the risk, compensation, protection, cost, benefits, and so on. *Fairness* is the result of a political balancing of scientific information and policy, which is outside the scope of the scientific assessment per se, but can contribute by elucidating these and other errors and by roughly accounting for the interests of different groups that may benefit or pay.

**Comment**

In the context of regulatory modeling, it is important to distinguish between model verification, validation, conformation, and calibration. A system can be verified, meaning that its truth can be ascertained, if it is closed (Oreskes et al., 1994). For such systems, it can be formally demonstrated that when the premises are true, the conclusions cannot be false (Oreskes et al., 1994). For example, verification is the correct term to use when demonstrating a theorem. However, verification does not apply to the forms of complex causation discussed in legal proceedings and in most risk assessments. The reason is that inductive inference, consisting of statistical analysis, cannot be deductively verified. Specifically, in risk assessment, decision-makers must deal with open systems that are characterized by assumptions that cannot be verified *a priori* (Oreskes et al., 1994). *Verification* in risk assessment and management is therefore a strong requirement that should be avoided in favor of less demanding terms.

*Validation* is the independent replication of results. Accordingly, validation focuses on the consistency of the system relative to what it attempts to portray, and includes empirical corroboration from other sources. Validation can include auxiliary assumptions (premises) that enhance it. Even when it meets logical, first principles and internal consistency, it is weaker than verification, which is truth determining and deductive. Validation *corroborates* empirical results through first principles and appropriate mathematical procedures: the mere agreement between alternative sources of data can provide increasing levels of approximations of the actual system being measured, but cannot guarantee an accurate representation of the physical system. When a numerical solution approximates an analytical solution, the approximation does not *verify* the numerical solution. The preferable term for this form of assessment is *benchmarking*. Validation procedures are especially useful for guiding decision-makers, because they help by including the possible confidence in the proposed model and analysis. This statement of confidence (for example, by accounting for predictive validity, as opposed to description of the data and process) is useful context for policy makers in deciding how to allocate resources.

*Confirmation* deductively assesses empirical results that are presumed to be generated by a scientific law. The concept that *science requires that empirical observations be framed as deductive consequences of a general theory* is the basis for what is generally understood as the confirmation of a theory (Oreskes et al., 1994). The strength of the confirmation increases as the number of very similar independent empirical results (stated as magnitude and direction of the relationships) increases. An issue with confirmation is

that if a model fails to reproduce observed data, then we know that the model is faulty in some ways, but the reverse is never the case (Popper, 1965). There are two meanings for the term *reverse*. One refers to Popper’s falsification: Popper’s tenet that it is not possible, even in principle, to prove that a theory is true. However, it is possible to prove that a theory is false. Thus, if a model reproduces observed data, we still do not know whether the model is correct in all respects. The second meaning of the term *reverse* is that models and data are uncertain. When a model fails to reproduce observed data, it is possible that the model is valid but that the observed data is faulty. Oreskes et al. (1994) have stated that *confirmation* is a matter of degree and that the central problem with the language of validation and verification is that it implies an either-or situation.

*Calibration* is the manipulation of the independent variables to obtain a match between the observed and simulated distribution of a dependent variable (Oreskes et al., 1994). Understood this way, calibration is a means, but not the ultimate means, to provide *empirical adequacy* to a particular theory. Refinements might be required to achieve an acceptable level of empirical adequacy. In practice, those refinements occur through *sensitivity analyses*. Sensitivity analyses are especially useful with regard to deciding which aspects of the model representation need to be understood better to provide the most useful information to decision makers. They guide the choice of additional data to gather, and the new data may or may not result in model refinement.

We suggest that where precaution and science are separated by assumptions and conjectures, the *empirical sufficiency* of the scientific evidence is perhaps the most relevant paradigm when trying to establish empirical causation. It depends on the state of the information and on methods to determine it at the time that the risk-modifying actions are being studied. Empirically sufficient evidence, such as the combination of relevant data and models, must be valid. Empirical sufficiency requires probabilities or other measures of uncertainty, and expert evidence to construct plausible models. However, empirical knowledge is probabilistic and conditional on what is known at the time. *Generalizability* of results and *necessary-for-purpose* may be all that is needed (and thus be sufficient) for risky decisions that must be taken under the precautionary principle, provided adaptability and resilience of the managerial choice. For risk assessment and management specifically, empirical sufficiency is a plausible basis for accepting the conceptualization, design, testing and generalizations of a dose-response model and its results.

**Precaution is Consistent, not Antithetic, with Hormesis**

We concur with Hanekamp and Bast, (2006, this issue of BELLE), in the context of the REACH (Registration, Evaluation, and Authorization of Chemical Substances) program, that the EU’s precautionary attempt to regulate chemicals in a comprehensive and very costly, with the specific use of the linear, no threshold model of dose-response at low dose often being unwarranted. Hanekamp and Bast, (2006, this issue of BELLE) state that:
“The acceptance of hormesis would in principle seriously attenuate the basics and ambition of REACH, especially the utopian ‘toxic free’ society. Despite the fact that REACH is specifically driven by precaution, in light of hormesis the precautionary principle itself does not justify the entertained default assumption at all. … Negative external costs of regulation are part and parcel of reality irrespective of regulatory interest and focus. The reality (by itself, and relative to the hypothesis of linearity at low dose, emphasis and comment added), of hormesis shows that REACH—once implemented—is far from precautionary …”

The flaw that we find with any regulatory attempt to limit exposure via the LNT hypothesis, or other precautionary approach, is that no beneficial effects are allowed; in fact, they are taken away even when several hundred test results show that those effects exist, are consistent over time and across different researchers, and are not spurious. Unverifiable and merely hypothetical noxious events drive costly regulation that denies any of those benefits and, somehow inexplicably, manages to overcome facts. When we consider the cost of REACH, the issue becomes mind-boggling, because (Hanekamp and Bast, op. cit., 2006), the

Costs estimates—scientific, regulatory and economic— for implementing REACH vary wildly; up to a 100 billion euro has been suggested. The European Commission estimates the costs to be 50 billion euro. There is now way of telling what the actual costs will be, yet the benefits have been estimated by the European Commission to be several thousand (statistical) human lives in Europe as a result of diminished environmental exposure to synthetic chemicals based on the default assumptions of the LNT (and LT) models.

If the certain (meaning demonstrated) benefits from hormesis are lost in favor of the hypothetical lives saved from REACH (“several thousands” statistical lives saved from among approximately 400,000,000 Europeans cannot be ascribed to REACH, other than probabilistically) are balanced, what is the net result and net effect of these expenditures on society already characterized by relatively high unemployment? Unfortunately, the argument hinging on employment reduction due to regulation is seen as a ploy by industrial interests. Therefore, it is essential to include hormesis in regulations. If hormetic responses exist for certain substances, then a zero-tolerance approach actually harms the population’s health. This harmful impact of zero-tolerance contradicts the precautionary principle; the simple-minded interpretation of the precautionary principle needs to be reexamined in light of hormetic processes to truly implement a precautionary approach. Clearly, the demonstrated benefits of hormesis should be weighed asymmetrically to any conjectured reduction in deaths (the indemonstrable thousands of lives saved by REACH). Any policy that affirmatively denies demonstrable benefits and yet attaches very high value (in the billions of euros) to conjectural results ought to be reexamined and, when shown to be contrary to sound public policy, either modified or replaced.

Let us consider another European example, summarized by Hanekamp and Bast (2006):

Accepted medical exposure to an EEC No. 2377/90-listed substance (Chloramphenicol, an antibiotic) can cause unintended adverse health endpoints (for instance, aplastic anemia with an estimated annual incidence of 1.5 cases/10,000,000 exposed, due from all causes) at permissible levels of medical exposure. On the other hand, exposures at much lower concentrations of this substance through residual levels of this antibiotic in foodstuff has not caused that (or other endpoints) such as leukemia; moreover, epidemiological results did not show risk of aplastic anemia. According to Hanekamp and Bast (2006), food residue exposures in shrimp, one of the main sources of human exposure, are 0.00000017 mg/kg body weight/day; yet, medical exposure is between 25 and 125 mg/kg body weight/day. Although there is a difference between voluntarily (informed) medical treatment and an involuntary and uniformed implicit acceptance of an exposure to an antibiotic in food, these exposures (differing by several orders of magnitude) and their consequences (from none to 1.0/10,000,000, not 1.5/10,000,000 exposed, as explained by Hanekamp and Bast (2006), are not commensurate. Yet, under EEC No. 2377/90, exposure to Chloramphenicol cannot be tolerated: fish products that contained that substance were either excluded from the European markets or destroyed.

Arsenic as a Regulated Carcinogen
Arsenic provides a useful example for understanding difficulties associated with hormetic responses and implementing proper policy in light of existing information. Regulators have ignored evidence of hormetic dose-response with arsenic and instead have shifted standards according to arbitrary model choice. Problems with this approach and suggestions for improving the approach to arsenic standards are detailed in this section.

Arsenic is a well-known toxicant; nonetheless, its regulation at low dose continues to produce considerable policy debate about the magnitude of the cost of compliance relative to the benefit measured by decreases in cancer risk. Calabrese and Baldwin have found hormetic responses associated with exposure to sodium arsenite (Calabrese and Baldwin, 2003b, Inorganics and Hormesis, Critical Reviews of Toxicology, 33:215–304) and describe three set of results in which a hormetic model represents animal response to exposures to this substance.

The essence of the scientific issue is the choice of the appropriate dose-response model for accurate science-policy (Snow ET, Sykora P, Durham TR, Klein CB, Arsenic, Mode of Action at Biologically
Plausible Low Doses: What are the implications for low dose cancer risks, Tox & App. Pharmacology, 2005, 207:557-564). An unpublished draft advisory report (Advisory on EPA’s Assessment of Carcinogenic Effects of Organic and Inorganic Arsenic, Dec. 27, 2005) regarding the carcinogenicity of this agent (as is inorganic arsenic), relevant to causal model building, states that:

There is a lack of adequate human data at the lower range of iAs due to limitations in epidemiologic studies conducted to date. …Studies in different populations across different countries … seem to support a possible linear dose-response between exposure from drinking water and internal cancer risks (particularly in Taiwan, Chile and Argentina). However, the dose-response relationships are observed at higher exposure levels (>100 ppb). Although some recent studies have included populations with exposures in the lower range (<100 ppb), they are not appropriate for using in dose-response analysis for lower exposure levels since they have problems related to study design, exposure assessment and statistical power. Estimations of low dose risk based on studies in populations with only low dose exposure are unstable with high uncertainty and studies are underpowered … There is no human data available that is adequate to characterize the shape of the dose response curve below a given point of departure.

The NRC (2001) used standardized mortality rates (SMRs) for males and females in its quantitative risk assessment of inorganic arsenic in water. We depict a non-parametric bivariate distribution of those data in Figure 1 to show that the relationship between the SMRs for males and females. The results depict positively correlated SMRs. The surface has two humps (the centers of the contours are higher than their surrounding contours).

Table 2. Example of dose-response models used to describe the risk of cancer from ingesting inorganic arsenic in water.

<table>
<thead>
<tr>
<th>Author, study type</th>
<th>Risk Ratios and Confidence Limits</th>
<th>Model</th>
<th>Cancer</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferreccio et al (2000), N Chile, case-control</td>
<td>OR: 2.4 (1.9, 2.9)</td>
<td>Linear regression</td>
<td>Lung, 1930 to 1994</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>OR: 1.4 (1.3, 1.5)</td>
<td>Linear regression</td>
<td>Lung, 1958 to 1970</td>
<td>M, F</td>
</tr>
<tr>
<td>Chiou et al (2001), NE Taiwan, prospective cohort</td>
<td>RR: 1.05 (1.01, 1.09)</td>
<td>Multiplicative, ln(dose)</td>
<td>Urinary, &gt;8,000 individuals</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>RR: 1.44 (0.63, 2.24)</td>
<td>Additive, linear dose</td>
<td>Urinary</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>RR: 1.21 (0.89, 1.64)</td>
<td>Multiplicative, lin(dose) (&lt;400 ppb)</td>
<td>Urinary</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>RR: 1.25 (0.89, 1.64)</td>
<td>Multiplicative, ln(dose) (&lt;400 ppb)</td>
<td>Urinary</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>RR: 1.47 (0.58, 2.36)</td>
<td>Additive, linear dose (&lt; 400 ppb)</td>
<td>Urinary</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>RR: 1.54 (0.81, 2.91)</td>
<td>Multiplicative, linear dose (&lt; 200 ppb)</td>
<td>Urinary</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>RR: 1.77 (0.21, 3.34)</td>
<td>Additive, linear dose (&lt; 200 ppb)</td>
<td>Urinary</td>
<td>M, F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.15 (1.10, 1.14)</td>
<td>Multiplicative, linear dose</td>
<td>Lung</td>
<td>M</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.15 (1.13, 1.18)</td>
<td>Multiplicative, ln(dose)</td>
<td>Lung</td>
<td>M</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.26 (1.25, 1.27)</td>
<td>Additive, linear dose</td>
<td>Lung</td>
<td>M</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.16 (1.14, 1.18)</td>
<td>Multiplicative, linear dose</td>
<td>Lung</td>
<td>F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.21 (1.18, 1.24)</td>
<td>Multiplicative, ln(dose)</td>
<td>Lung</td>
<td>F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.46 (1.44, 1.49)</td>
<td>Additive, linear dose</td>
<td>Lung</td>
<td>F</td>
</tr>
<tr>
<td>Chen et al (1985, 1992), SW Taiwan</td>
<td>1.22 (1.19, 1.24)</td>
<td>Multiplicative, linear dose</td>
<td>Bladder</td>
<td>M</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.29 (1.26, 1.33)</td>
<td>Additive, linear dose</td>
<td>Bladder</td>
<td>M</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.98 (1.92, 2.14)</td>
<td>Multiplicative, ln(dose)</td>
<td>Bladder</td>
<td>M</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.25 (1.23, 1.28)</td>
<td>Multiplicative, linear dose</td>
<td>Bladder</td>
<td>F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>1.34 (1.31, 1.38)</td>
<td>Multiplicative, ln(dose)</td>
<td>Bladder</td>
<td>F</td>
</tr>
<tr>
<td>Ibid.</td>
<td>2.57 (2.42, 2.73)</td>
<td>Additive, linear dose</td>
<td>Bladder</td>
<td>F</td>
</tr>
</tbody>
</table>

Figure 1. Bivariate polynomial fit to male and female SMRs from arsenic.

A summary of the epidemiological studies of waterborne arsenic exposure and response, risk measures, and models indicates that several different model forms have been tested; those models include linear regression, multiplicative ln(dose), additive ln(dose), additive linear dose, and multiplicative linear dose (Table 2).

The results from Chiou et al. (2001) are generally statistically insignificant, other than for a case in which the model, with additive dose, is used (the 95% CI about the $RR = 1.05$ is 1.01 to 1.09; the hypothesis of no effect between the incidence of the disease in the exposed and the incidence of the disease in the unexposed is that the $RR = 1.00$).
Individual water ingestion varies considerably between the Taiwanese and Americans. The NRC (2001) conducted a sensitivity analysis varying the amount of water from 1.0 liter to 3.0 liters per day. For data from SW Taiwan males, using the BEIR IV formulae for $ED_{01}$, the estimated $ED_{01}$ ranged from 65 mg/l of arsenic to 246 mg/l; the lower 95% confidence limits varied from 41 to 173 mg/l of arsenic. Further analyses, (NRC, 2001) using the Poisson and Bayesian methods to account for errors-in-variable, showed that the $ED_{01}$ and lower 95% confidence limits were much more stable (142 to 145; and 125 to 129 mg/l of arsenic).

The NRC used the Morales et al. (2000) Model 1 to calculate the $ED_{01}$ excess lifetime incidence per 10,000 of lung and bladder cancer for the general US population. The $ED_{01}$ is the effective dose that results in a 1% increase in the lifetime individual risk of cancer over background. This table depicts the estimates of excess lifetime cancer risks (Incidence/10,000) based on $ED_{01}$ numbers developed from Morales et al. (2000) using a Poisson regression model (NRC, 2001):

<table>
<thead>
<tr>
<th>Arsenic in water (micrograms/liter)</th>
<th>Bladder Cancer</th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>0.76</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>10</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>20</td>
<td>7.9</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Table 3. Excess Cancer Mortality from Ingestion of Waterborne Inorganic Arsenic.

**Comment on Inorganic Arsenic and Cancer**

Funnel plots are scatter plots in which the treatment effects estimated from individual studies are plotted as a function of their precision (Light and Pillemer 1984). Usually, the horizontal axis corresponds to the treatment effect estimates. In the absence of bias the graph resembles a symmetrical inverted funnel because: 1) the treatment effect estimates from smaller studies scatter widely at the bottom of the graph; and 2) the spread narrows with the increasing precision characteristic for larger studies. For example, if there is a publication bias because smaller studies showing no statistically significant effects remain unpublished (Easterbrook et al., 1991; Dickersin et al., 1992), then the funnel plot is asymmetrical (Begg and Berlin 1988; Egger and Davey-Smith 1995). Moreover, funnel plot asymmetry could result from the overestimation of treatment effects in smaller studies of inadequate methodological quality (Schulz et al. 1995). Heterogeneity of treatment effects leads to funnel plot asymmetry if the true treatment effect is larger in smaller studies (Egger et al. 1997; Sterne et al. 2000). If asymmetry is present, likely reasons should be explored; although funnel plots may flag a problem that needs to be addressed, they do not provide a solution to the problem.

We quantified the treatment exposure effect through the natural logarithm of the odds ratio (cancer present vs. absent). Following Sterne and Egger (2001) we used an inverted vertical axis for the standard error of the treatment effects. The results plotted below are based on the data of Ferecchio et al., (2000), Chiou et al. (2001), and Chen et al. (1985, 1992). The Egger test (Egger et al., 1997) detects (at 95% confidence level) a significant asymmetry of the funnel plot (Figure 3).

Given the overall information reviewed: What are the implications for choice of model of dose response? The US EPA’s Scientific Advisory Board (SAB) answer is equivocal because it does not indicate how competing models can be weighted and combined:

At present the experimental evidence on mode of action of inorganic arsenic supports a possible non-linear dose-response at low exposure levels yet there is no clear indication of what shape a non-linear dose-response would take for application to human cancer risks at low exposures (<50 or 100 ppb). In examining the dose response relationships of arsenicals in response inducing mutagenic responses (including effects thought to be clastogenic), it
is clear that effects are only seen at doses that induce cytotoxicity. This implies a threshold. Until more is learned about the complex properties and MOAs [Modes of Action] of iAs and its metabolites there is insufficient justification for the choice of a specific non-linear form of the dose-response relationship. Under these circumstances, the EPA's 2005 Guidelines for Cancer Risk Assessment are clear that linear extrapolation below the low point of departure is the method to be used. Although the EPA has chosen a linear model for the arsenic dose component of the hazard model for lung and bladder cancer, the Panel encourages the Agency to test the sensitivity of the assumption of linearity by comparing its corresponding estimate of excess lifetime risk to an alternative hazard model that has a dose contribution that is multiplicative and quadratic form. In summary, the Panel recognizes the potential for a highly complex mode of action of iAs and its metabolites, but until more is learned about the complex PKPD properties of iAs and its metabolites there is insufficient justification for the choice of a specific nonlinear form of the dose-response relationship. Based on this and the EPA’s 2005 Guidelines for Cancer Risk Assessment, the final recommendation of NRC (2001) to base current risk assessments on a linear dose response model that includes the SW Taiwan population as a comparison group seems the most appropriate approach. However, the Panel also recommends a) perform performing a sensitivity analysis with different exposure metrics with the subgroup of villages with more than one well measurement; b) using a multiplicative model that includes a quadratic term for dose, as performed by NRC (2001).

A non-linear dose-response includes a threshold as a special case. It is not clear what it is meant by “possible” in the sense of clarifying what is probable (with probability $p$) and its complement, the improbable (with probability $1-p$). It seems that the non-linearity is to be accounted, but not the threshold. At the causal level, the SAB suggests adding a quadratic term and a cross product term in the dose-response and perform a sensitivity analysis: this is not the theoretically correct way to choose between competing models (Cox, 2002; Cox and Ricci, 2004). Given that the use of arsenic data to form policy has been based on a biased use of the data, it is essential that this topic is revisited. The example of arsenic might be a good choice of a trial case for possible inclusion of hormesis in decision-making.

Conclusions/Recommendations

We have demonstrated that consideration of hormesis is consistent with the precautionary principle that underlies much of EU and US regulation. Failure to consider demonstrated hormetic dose-responses in favor of arbitrary linear zero-threshold models is in fact antithetical to the precautionary principle. The use of these LNT models could result in not only misallocation of resources, but also unwitting damage to public health that defies the precautionary principle.

Due to the entrenchment of historical zero-tolerance approaches, we do not recommend that an immediate, all-encompassing change occur. Instead, agencies should develop procedures and processes for evaluating hormesis and then incorporating any existing evidence into regulations. As a first step, one substance with demonstrated hormetic behavior should be regulated in a manner that considers the hormetic model. This trial balloon will effectively allow scientists and regulators to iron out any unforeseen difficulties as well as provide an opportunity to inform the public without causing a large backlash before the public becomes educated about hormetic behavior. If regulating this first substance is successful, then adjusted regulation of additional demonstrated hormetic substances can follow.

References


RESPONSE TO COMMENTATORS

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First of all, we would very much like to thank the commentators for their remarks on our paper. It gave us plenty food for thought. The focus in our paper is the precautionary principle (or precautionary approach), which seems historically and toxicologically implicitly or explicitly one of the main drivers of increasing stringent chemical policy-making in the past decades. We have taken the principle as the linchpin of precautionary culture we regard as a pervasive aspect of (post-)modernity. Two of main extrapolating toxicological models –the LT and LNT model- seem to fit precautionary culture quite well, as these models can address the moral perspective on synthetic chemicals most effectively. Moreover, we envisage that acceptance of the hormesis model both in toxicology and regulation will be more than data gathering; the issue of authority within science and government and the choice of the research focus, development, application and justification influenced by precautionary culture, seems more important.

The three papers we have received comment primarily on our critique of precautionary culture, albeit in different ways. Morris, for instance, although he is in large part in agreement with our analysis, thinks we take precaution too far. Quoting Sunstein, Morris asserts that ‘Simply as a logical matter, societies, like individuals, cannot be highly precautionary with respect to all risks. Each society and each person must select certain risks for special attention’. However, we do not take precautionary culture to be pervasive because every, and all risks are addressed in a precautionary manner. On the contrary, the cognitive availability (personally and institutionally) would indeed limit as a whole different responses to risk (especially as a result of policymaking), whether precautionary or not. We do take precautionary culture to be pervasive because risks of the overtly technological kind are viewed with suspicion, and the demand for stringent regulation of those risks has, especially in Europe, an importunate precautionary nature. As Western society has become increasingly technological, the demand for an equal and fair distribution and reduction of diminishing (long-term) risks has risen (dis)proportionally. In our paper we have given some examples, and especially REACH, as an overarching policy that will influence not only the primary chemicals industry but also many adjacent industries, is a prime example we have discussed. Jostman is in agreement with our analysis, yet could have been more explicit in terms of the industrial regulatory alternative to REACH apart from the incorporation of hormesis as opposed to the well-known defaults.

Ricci and MacDonald do not see a conflict between hormesis and precaution. Their response makes for stimulating reading. For one, they approach the precautionary principle symmetrically, wherein the goal of regulation –say human health- can be harmed when based on ‘arbitrary linear zero-threshold models’, which they regard as ‘in fact antithetical to the precautionary principle’. Obviously, we fully agree here. However, in their discussion on facts versus conjectures they put forward a view of science, in which the principle of proportionality –that is the firmness with which one accepts a belief or a theory is, at all times, in proportion to the strength of the evidence for it- and Popper’s proxy the principle of tentativity –all rational beliefs or theories should only be accepted tentatively in lieu of the never-ending search for counter-evidence- with reference to Oreskes et al. have centre stage. Models and theories can only cater for a relative epistemic safety.

The problem we have with this description of models is that commitment to scientific models and theories to all intents and purposes seems far stronger than the principles of proportionality and tentativity would suggest or even allow for. Indeed, relative epistemic safety would waste too much of our intellectual resources. Successful scientific work requires full commitment (not, however, of the dogmatic kind!); proportionality and tentativity endanger the modus operandi of science itself as the institution of science could hardly survive if most members of that community would continuously aim at falsifying theories or only partially involve themselves with the theories they work on. When it would be so that scientists as scientists do not believe the theories they themselves work on and work with, then our propensity to believe their commitments is in danger of being an improper application of science. As Newton-Smith remarks in The Rationality of Science ‘Progress requires that most scientists get themselves in the grip of a theory which they aim to develop and defend, and without simply trying to dispose of it as fast as possible.’

In relation to the issue of precaution, theory-commitment comes forward most poignantly in the rejection of hormesis for instance by Axelrod et al but also by the EPA. This rejection of hormesis is a clear indication that tentativity and proportionality is not part of the reality scientists usually are confronted with inside and outside the lab. Likewise, reasons to adhere to linear models within the context of precaution probably are more related to the non-epistemic characteristics of the cultural ecological critique and its conservative moral. Hormesis would in risk assessment and –management terms allow for the presence of synthetic chemicals in for instance the environment and food, which is counter to most environmental and food-safety policies, REACH being the prime example. Yet, explaining one’s theory-commitment non-epistemically is not a preferred interest within the scientific community.

‘We suggest that where precaution and science are separated by assumptions and conjectures, the empirical sufficiency of the scientific evidence is perhaps the most relevant paradigm when trying to establish empirical causation’ is the proposed solution by Ricci and MacDonald to bridge the gap between science and precaution. Again, although we do sympathise with this approach, this requires a confrontation with the non-epistemic part of theory-commitment, which does not seem a straightforward task. However, in order to
get forward with the task of knowing (even if only by approximation) the toxicological reality (obviously we here expound a critical realist perspective) we do believe (sic!) that empirical sufficiency can only function properly within the context of full theory-commitment. As the history of hormesis shows, the data do not speak for themselves.

In conclusion, we contend that hormesis, as do all commentators, should have a place in regulation. This is in line with a full–weight–of–evidence approach ideally developed in risk assessment procedures. The European and the American society should be weary of the danger in setting up open–ended compulsorily regulatory structures particularly advanced by the precautionary principle. Few could resist expanding on the ‘exigencies of public health’ if given official normative powers and unrestrained license to define. Obviously, the remarks made here contain (non-epistemic) value–judgements, which, however, need not be eschewed in view of the costs and benefits of chemicals regulation.

REFERENCES

1 To whom correspondence should be addressed: hjiap@xs4all.nl +31(0)793460304.
13 Hanekamp, J.C., Verstegen, S.W., Vera–Navas, G. The historical roots of precautionary thinking: the cultural ecological critique and the
PLATFORM PRESENTATIONS
TUESDAY, JUNE 6, 2006

Morning
8:30am – Noon  Campus Center Auditorium

Session I: PLENARY
Moderator:  Paul Kostecki, University of Massachusetts, Amherst, MA

8:30am  Phytochemical Hormesis
Mark P. Mattson, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD

9:15am  Biphasic Dose-efficacy in Antiangiogenic Therapy
Judah Folkman, Children's Hospital Boston, Boston, MA

10:00am  Break  163C Campus Center

10:30am  How Does the Concept of Adaptive Response In Radiation Relate to the Concept of Radiation Hormesis?
Ron Mitchel, Chalk River Laboratories, Chalk River, Ontario, Canada

11:15am  Hormesis in Carcinogenesis: Evidence for a Threshold in Carcinogenicity of Non-genotoxic Environmental Carcinogens
Shoji Fukushima, Osaka City University Medical School, Osaka, Japan

Noon LUNCHEON SPEAKER 1009 Campus Center
THREE MILE ISLAND: A CASE FOR WHY WE NEED GOOD HISTORY
J. Samuel Walker, Ph.D., Historian, US Nuclear Regulatory Commission, Washington DC

Afternoon
1:30pm – 5:00pm  Campus Center Auditorium

Session II: RADIATION
Moderators:  Bobby Scott, Lovelace Respiratory Research Institute, Albuquerque, NM
            Carmel Mothersill, McMaster University, Hamilton, Ontario, Canada

1:30pm  Protective Bystander Effects Following Low Dose Ionizing Radiation Exposure
Carmel Mothersill, M. Kilemade, W. Prestwich, Alicia O’Neill, Zhongfeng Liu, CB Seymour, McMaster University, Hamilton, Ontario, Canada

2:00pm  Adaptive Response in pKZ1 Mouse Prostate after Whole Body Exposure to Very Low X-Radiation Doses
Tanya Day, Gouxin Zeng, Antony M. Hooker, Flinders University and Medical Centre, Bedford Park, Australia; Madhava Bhat, Adelaide Radiotherapy Centre, Adelaide, Australia; David R. Turner, Pamela J. Sykes, Flinders University and Medical Centre, Bedford Park, Australia

2:30pm  Radiation-Induced Neoplastic Transformation In Vitro, Hormesis and Risk Assessment
Leslie Redpath, University of California Irvine, Irvine, CA

3:00pm  Low Dose Radiation Exposure and Modulation of High Dose Effects on Embryogenesis and Heritable Mutations
Douglas R. Boreham, McMaster University, Hamilton, Ontario, Canada

3:30pm  Break  163C Campus Center

4:00pm  Prolongation of Life Span of Disease Model Mice by Low Dose Rate Irradiation
Kazuo Sakai, Central Research Institute of Electric Power Industry, Tokyo, Japan

4:30pm  Biological System Response to Ionizing Radiation Invalidates the Linear-no-Threshold-Hypothesis
Ludwig F. Feinendegen, Brookhaven National Laboratory, Upton, NY and Heinrich-Heine-University, Dusseldorf, Germany; Myron Pollycove, School of Medicine, University of California San Francisco, San Francisco, CA; Ronald D. Neumann, National Institutes of Health, Bethesda, MD

5:00pm  Smoking and Hormesis as Confounding Factors in Radiation Pulmonary Carcinogenesis
Charles L. Sanders, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea

6:00pm  DINNER  1009 Campus Center
Morning
8:30am – 11:30am Campus Center Auditorium
Session III: TOXICOLOGY
Moderator: James E. Klaunig, Indiana University of Medicine, Indianapolis, IN
8:30am Oxidative Stress: Dose Responses and Application to Hormesis
Lisa Kamendulis, Indiana University School of Medicine, Indianapolis, IN
9:00am Arsenic Induced Hormesis: Underlying Mechanisms and Timing
Elizabeth T Snow, Troy R Durham, Robert M Kozlovske, Robert Sykora, Deakin University, Bunwo, VIC Australia
9:30am Unraveling the Mechanisms behind Hormesis in Plants
Nina Cedergreen, Jens C. Streibig, The Royal Veterinary and Agricultural University, Taastrup, Denmark; Stephen O. Duke, USDA, University of Mississippi, University, MS
10:00am Break 163C Campus Center
10:30am Hormesis Model Dominates Threshold Model in Large Scale NCI Anti-tumor Drug Screening Data
Edward J. Calabrese, Edward J. Stanek III, John W. Staudenmayer, University of Massachusetts, Amherst, MA; George R. Hoffmann, Holy Cross College, Worcester, MA
11:00am Nonlinear Dose-Response Mechanisms – Simulation with Bio-Mathematical Models
Helmut Schöllnberger, University of Salzburg, Salzburg, Austria; Ronald E.J. Mitchell, Chalk River Laboratories, Chalk River, Ontario, Canada; Douglas J. Crawford-Brown, UNC, Chapel Hill, NC; W. Hofmann, University of Salzburg, Salzburg, Austria
Afternoon
1:30pm – 5:00pm Campus Center Auditorium
Session IV: PRACTICAL ISSUES WHEN USING HORMESIS IN RISK ASSESSMENT NOON
Moderator: Mike Dourson, TERA, Cincinnati, OH
1:30pm Risk Assessment and Recognizing Hormesis during Hazard Identification
Beth Doyle, EPA, Washington D.C.
2:00pm Incorporating Mode of Action Understanding of Hormesis into Dose Response Assessment
Lynne T. Haber, Andrew Maier, Michael L. Dourson, Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH
2:30pm Fluoridation as a Case Study in Hormesis
Dennis Jones, ATSDR, Atlanta, GA
3:00pm Meta-Hormesis for Uncertain Risks: Arsenic as a Case Study
Louis Anthony (Tony) Cox, Jr., Cox Associates, Denver, CO
3:30pm Break 163C Campus Center
4:00pm Detailed Case Study of Hormesis for Radiation
Colin Seymour, McMaster University, Hamilton, Ontario, Canada
4:30pm Open and Panel Discussion on the Practical Issues of using Hormesis in Risk Assessment
Lead by Michael Dourson, TERA, Cincinnati, OH
6:00pm DINNER 1009 Campus Center
Annual Meeting of the International Hormesis Society

LUNCHEON SPEAKER
STRESS RESPONSE MECHANISMS: FROM SINGLE CELLS TO MULTINATIONAL ORGANIZATIONS
Richard J. Pech, Ph.D., Director of Research at the Graduate School of Management, La Trobe University, Melbourne, Australia

THURSDAY, JUNE 8, 2006
Morning 8:30am – Noon Campus Center Auditorium
Session V: BIOMEDICAL
Moderator: John Ives, Samueli Institute, Alexandria, VA
8:30am Memory Molecules and Hormones
John E. Morrey, Susan A. Farr, Saint Louis University Health Sciences Center, St. Louis, MO
9:00am Biphasic Dose Response of Steroid Hormone Action
Roberta Diaz Brinton, University of Southern California, Los Angeles, CA
9:30am Role of Hormesis in Life Extension by Caloric Restriction
Edward Masoro University of Texas Health Science Center, San Antonio, TX
10:00am Break 163C Campus Center
10:30am Hormesis, Control Theory, and Substance Use Disorders
David B. Newlin, RTI International, Baltimore, MD
11:00am Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer
Bobby Scott, Jennifer Di Palma, Lovelace Respiratory Research Institute, Albuquerque, NM
11:30am Streptolyses O Enhances Keratinocyte Migration and Proliferation and Promotes Skin Organ Culture Wound Healing
Marjana Tomic-Canic, Hospital for Special Surgery, New York, NY; Stephen W. Mamber, Beech Tree Labs, Delanson, NY; Olivia Stojadinovic, Hospital for Special Surgery, New York, NY; Brian Lee, Genentech, San Francisco, CA; Nadezda Radoja, NIAMS, Bethesda MD; John McMichael, Beech Tree Labs, Delanson, NY
Poster Session A partial listing
163 C Campus Center for the duration of the conference. Authors will be available during the session breaks.

LDR Does not Induce Adaptive Response in Tumor Cells
Lu Cai, University of Louisville School of Medicine, Louisville, KY

Empirical Models for Hormesis
Nina Cedergreen, The Royal Veterinary and Agricultural University, Taastrup, Denmark; Christian Ritz, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark; Jens Carl Streibig, The Royal Veterinary and Agricultural University, Taastrup, Denmark

Identifying Non-linear Radiation Dose Responses In Vivo: Exploring Bystander Effects
Benjamin J. Blyth, Tanya K. Day, Pamela J. Sykes, Flinders University and Medical Centre, Bedford Park, South Australia

Expected Lives Saved due to Medical, Therapeutic, Environmental and other Forms of Radiation Hormesis
Jennifer Di Palma, Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM

Effects of Low Doses of Dietary Lead on Red Blood Cell Production in Three Successive Generations of Swiss Mice
Ivo Iavicoli, Giovanni Carelli, Catholic University of Sacred Heart, Rome, Italy

Hormesis as a Confounding Factor in Epidemiological Studies of Radiation Carcinogenesis
Charles L. Sanders, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea
Call For Papers

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For further Information contact
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INTERNATIONAL HORMESIS SOCIETY  
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GOAL
A growing number of scientists, including toxicologists, pharmacologists, biostatisticians, epidemiologists, occupational and environmental medical researchers and others have begun to display considerable interest in the topic of hormesis, a dose response phenomenon characterized by a low dose stimulation and a high dose inhibition. While there are many professional societies that have a general interest in dose response relationships, none explicitly is devoted to the topic of understanding the nature of the dose response in general and hormesis in particular. The diversity of professional societies that may consider dose response issues, including hormesis is nonetheless quite broad ranging from the agricultural to the biomedical and clinical sciences. However, nearly without exception, these societies tend to be strongly organized around professional advancement and not focused on specific scientific concepts. This makes the issue of hormesis one of diffuse interest across a broad range of professions. The present situation represents a major obstacle for the integrated assessment of the dose response in general and hormesis in particular. In order to provide intellectual and research leadership on the topic of hormesis, a new professional association has been created called the International Hormesis Society (IHS).

The Society will be dedicated to the enhancement, exchange and dissemination of ongoing global research efforts in the field of hormesis. In addition, the Society will also strongly encourage the assessment of the implications of hormesis for such diverse fields as toxicology, risk assessment, risk communication, medicine, numerous areas of biomedical research, and all other biological disciplines including relevant engineering domains dealing with the dose response.

LOCATION
The International Hormesis Society is administered by BELLE, School of Public Health & Health Sciences at the University of Massachusetts at Amherst.

MEMBERSHIP
The ISH is a professional society designed to enhance understanding of the nature of the dose response and its implications for science and society. Those individuals with a professional interest in these areas will be eligible for membership. Applicants for membership must complete the attached membership application form. Corporate memberships are $5,000.00 (U.S.) per year while Individual membership are $125.00 (U.S.) per year. Student memberships are encouraged with an annual dues set at $10.00. Applications should be mailed to the BELLE Office, Environmental Health Sciences Program, Morrill I, Room N344, University of Massachusetts, Amherst, MA, 01003.

As part of IHS membership, each corporate and individual member will receive a subscription to the journal Dose-Response (formerly called Nonlinearity in Biology, Toxicology and Medicine), which is currently a peer-reviewed quarterly journal. In addition there will be a Society Newsletter developed for the membership. There will also be an annual conference to which all society members will receive a reduction in registration fees.
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