

Hormesis in precautionary regulatory culture: models preferences and the advancement of science.

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Abstract

Introduction

'It is generally accepted that there can be numerous changes to the recipient organism following exposure to a chemical, some of which may be beneficial, adaptive, early manifestations on a continuum to toxicity, overtly toxic, or several of these things in combination. Unless there are data to indicate otherwise, a change that is considered adverse (i.e., associated with toxicity) is assumed to indicate a problem for humans.

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.

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The 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.³ 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 politicisation 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.⁴ 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.⁵) Especially relevant is the erosion of the classic and related modern ideals of autonomous knowledge and autonomous law.⁶ 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.⁷ Agreement on both facts and values have become an integrated whole.⁸

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*.⁹ 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.¹⁰ 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.¹¹ The *status quo* of the high standard of living in the Western world is thereby directly the publicly desired outcome of numerous types of regulation on all regulatory fields.¹² Public reluctance towards regulatory attenuation is therefore a common feature of Western precautionary culture.

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.¹³ 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.¹⁴ The precise content and meaning and therefore the best way to formulate the principle are also still a matter of intense dispute.¹⁵ However 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.¹⁶ 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:¹⁷ '... 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'.¹⁸

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 envisioned uncertain future adverse consequences of particular human activities.¹⁹ However, Stone for instance 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.'²⁰ 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.'

As is shown by the Rio definition, precaution is strongly related to environmental issues. Indeed, an earlier version of the Rio definition was defined in the 1987 *London Declaration* and focused on the environmental protection of the North Sea. The precautionary principle impresses upon us a moral obligation to take care of the environment, of mankind, our children, and our children's children. It therefore carries a profound intergenerational perspective on anthropogenic activities and its potential risks. The rise of the precautionary principle is therefore strongly related to so-called 'green thinking', which found its way to the centre of political power in the 1970s.

Bramwell, in her study on the ecological movement in the twentieth century, probes the development of green thinking and its impact on Western society.²¹ She firmly positions the rise of green thinking to political power in the early seventies of the twentieth century when the cultural ecological critique merged with the scientific economic concept of non-renewable resources. The conservative moral and cultural ecological critique combined with a recognisable scientific basis has rendered 'green thinking' the powerful political force it is today.²²

Here we use 'ecology' and 'ecological' in the normative political sense. It encompasses the belief -part and parcel of the mental furniture of most people in the Western world- that a man-induced drastic change within the environment is wrong and should be amended. Ecology is therefore associated with conservation, sustainability and precaution.²³ Green thinking on the one hand postulates 'wrongness' about Western industrialised society in for instance its use of finite resources its pollution potential and its concomitant risk for human health, and on the other hand sees part of the solution in a reorganised society in which these resources could be used more efficiently whereby environmental contamination could be curbed.

Green thinking combines pessimism about human nature –e.g. the freedom of trade and doing scientific research- with a misanthropic view on society and the competence of people to choose the 'right' government. This overt double pessimistic perspective on humans and human society spawned –not surprisingly- non-governmental institutions by which a 'green society' was to be accomplished. Sanguinity about human possibilities to reshape society, albeit in a radically different political context, obviously came forth from the then prevailing notion of utopian social engineering.²⁴

The precautionary principle's original rationale was to counter-balance the reluctance to take protective environmental and/or public health measures if absolutely proof of harm of some product or process could not be presented. Taken to its logical extreme, obviously, such an attitude will result in indefinitely continuing the status quo, because it is always possible to identify some remaining

uncertainty. Even if more and more evidence of harm comes forward and consensus on a cause-effect relation exists, any remaining uncertainty, even though very small, can still be used as a reason for not intervening. In its original meaning the principle stipulates that regulators may not demand the impossible, e.g. absolute proof of harm. However, the precautionary principle is now mostly understood and used in such a way that it mirrors the 'original sin' that it was designed to counter, namely an 'absolute proof of safety'. The principle itself and its application in society –reminiscent of the social engineering ideal we will mention further below with regard to REACH- have created numerous problems we will discuss here in short and has been put forward by many others.²⁵

One obvious quandary with precaution as defined in the Rio declaration is related to the issue of cost-effectiveness of regulation in the face of uncertainty (lack of knowledge of causality). What the principle's definition shows is that cost-effective measures are prerequisite in precautionary regulation. Cost-effectiveness in terms of precautionary regulation is however meaningless, as calculable regulatory costs are devoid of the context of benefits when causality is lacking. 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.²⁶ Indeed, considerable scientific evidence suggests that expensive regulation targeted at a specific risk has adverse effects on human life and health.²⁷ It is by no means precautionary to induce fatalities as a result of regulatory expenditure (that might subsequently also generate opportunity costs).

Therefore, the principle by definition leads in no direction whatsoever. The reason is that risks (and the 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.²⁸ The regulatory cost-induces fatalities issue is exemplary here. 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.²⁹

One telling example is the future-generations argument, which is presented fervently in relation to the principle.³⁰ However, who could legitimately claim to know in advance what future generations want the present generation to do? The ancient Greeks had a word for this attitude: *hybris*. If it is at all a sensible proposition to consider, then there is an *a priori* case against precaution, because it seems extremely unlikely that a substantial part of the present generation would have preferred their forefathers to be more precautionary in the development of our present technologies.

The precautionary principle thus cannot tell us what to do, only that a cautious route into the future is compulsory. It instructs us not to embark on a course without firm and final safety guaranties, but because all actions involve some risks, it does not help us to choose at all. Analysed at this logical level, the precautionary principle puts us in an impossible position: we have to decide on a safe course, but all options present us with uncertain risks. In other words: the principle tells us to act and not to act.³¹ To break this deadlock proponents of the precautionary principle resort to a limited application of the principle. By arbitrarily selecting some target risk and focusing exclusively on that risk, regulators can seemingly make a decision as to a perceived proper course of action resulting in policies that are blind for the negative external effects they create.

An example of arbitrary risk selection is the exclusive miscellany of man-made chemicals under the EUs REACH program, while there is no valid reason to exclude natural chemicals categorically from research into their dangerous properties.³² Even worse is the choice of the WHO to make unknown and most likely trivial risks of chemicals in toys or the environment a key target of its policy to promote children's health.³³ It is hard to comprehend this choice when the WHO shows in its own atlas of children's health that very real risks are still not addressed adequately or at all.³⁴

Of science, courts and law: a European precautionary tale

A recent example in Europe that encapsulates abovementioned flaws of the precautionary principle is the Antibiotic Growth Promotor (AGP) ban. Ricci *et al.* in the latest Belle Newsletter shortly discuss this issue, albeit only as a health issue. Antibiotics, when added to animal feed in small sub-therapeutic amounts, decrease the time and the amount of feed needed to reach slaughter weight. Furthermore, as the animals require less feed, manure excretion is lower. Moreover, the animals stay healthy and shed less pathogenic zoonotic organisms.³⁵ The use of these antibiotics had therefore a rather significant impact on the economics of animal rearing. It has been shown, however, that the use of antibiotics for this goal selects for resistant bacteria in animals.³⁶

Some of the growth promoters used in feed are structurally related to antibiotics used in human medicine. Their mode of action on bacterial cells can be identical (or highly comparable). Resistant bacteria found in animals might in this way be resistant to antibiotics used in human medicine. This is called cross-resistance. The concern was in the EU that resistance, as found in animals treated with growth-enhancing antibiotics, might spread to humans. This spread might add to the already widespread existence of bacterial resistance within humans resulting from human use of antibiotics.

On December 17th, 1998, the EC banned the use of four antibiotics as AGP additives in animal feedstuffs: virginiamycin, bacitracin zinc, spiramycin and tylosin phosphate. At the time the ban was adopted, no link had been proved between use of the antibiotics concerned and the development of resistance to those antibiotics in humans.³⁷ It was against that background that the Council of Ministers, on the recommendation of the European Commission, had recourse to the precautionary principle.

When the Council regulation was adopted, Pfizer Animal Health SA ('Pfizer') was the only producer of virginiamycin in the world. Pfizer brought an action for annulment of the regulation, which effectively prohibited the sale of the product in the European Union, before the Court of First Instance of the European Communities ('CFI'). At the time when the contested regulation was adopted, scientific views on whether virginiamycin constituted a risk to human health varied; some scientists and specialist bodies (WHO, Netherlands Health Council) considered that it did, while others (the SCAN,³⁸ and the experts called by Pfizer) did not. More specifically, the former group of scientists held the view that it was desirable to phase out a practice, which could contribute to the growth of antibiotic resistance in humans. The latter group held the view that there was no evidence that such a contribution had ever occurred, and that epidemiological indicators, after decades of use, offered no support for the proposition.

The CFI referred to the conclusions of these different specialist bodies and experts only in order to show the difference of opinion within the scientific community. The ruling makes no reference to the quality of the content of the scientific argumentation. The Court noted the existence of the controversy, but held that it was not for the Court to decide whether one side or the other's views were more plausible. Concerning the scientific debate, the Court stated the following:³⁹

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Relying on the SCAN opinion and the advice of Professor Casewell and Professor Pugh, Pfizer has, admittedly, put forward a number of factors which could be advanced to counter the argument that there is a link between the use of virginiamycin as an additive in feedingstuffs and the development of streptogramin resistance in humans. In particular, Pfizer has drawn attention to research in France and in the United States which shows that in those countries streptogramins continued to be very effective although virginiamycin had been used there as an additive in feedingstuffs for many years. Similarly, Pfizer maintained that some bacteria had a certain level of natural resistance, which was one plausible explanation for the level of streptogramin resistance observed.

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However, Pfizer does not claim that those arguments prove conclusively that there is no link between the use of virginiamycin as an additive in feedingstuffs and the development of streptogramin resistance in humans. They merely demonstrate that the existence of such a link is

'very unlikely' and that other 'plausible explanations' existed. Furthermore, the Council and the interveners challenged the merits of Pfizer's arguments relying, in their turn, on experts.'

Despite these remarks, the Court continued:

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It is not for the Court to assess the merits of either of the scientific points of view argued before it and to substitute its assessment for that of the Community institutions, on which the Treaty confers sole responsibility in that regard. In the light of the foregoing, the Court nevertheless finds that the parties' arguments, supported in each case by the opinions of eminent scientists, show that there was great uncertainty, at the time of adoption of the contested regulation, about the link between the use of virginiamycin as an additive in feedingstuffs and the development of streptogramin resistance in humans. Since the Community institutions could reasonably take the view that they had a proper scientific basis for a possible link, the mere fact that there were scientific indications to the contrary does not establish that they exceeded the bounds of their discretion in finding that there was a risk to human health.'

The Court of First Instance ruled on the basis of precaution, the essence of its conclusions being as follows:⁴⁰

'Despite uncertainty as to whether there is a link between the use of certain antibiotics as additives and increased resistance to those antibiotics in humans, the ban on the products is not a disproportionate measure given the need to protect public health.'

The Court relied on the precautionary principle to uphold the ban, as human health was said to be at stake albeit reviewed only in relation to the use of AGPs. That a ban could result in countervailing risks –growing curative use of antibiotics in animal rearing,⁴¹ an increase in imports of animal products from other countries where growth promoters are allowed and so on– was not considered by the Court. The arbitrary limited application of precaution surfaces here poignantly.

The ruling implies unreservedly that precautionary policies are axiomatically assumed to actually reduce risk. In other words, the principle is regarded as 'directional' in terms of risk reduction (in this case by imposing a ban), which however emerges *deus ex machina* in relation to the issue at hand as no serious empirical scrutiny is in order. Indeed, the Court found that the weight of authority, in the form of the positions held by those adhering to the resistance-transfer thesis, added to the credibility of that thesis. Yet the basis of science is something quite different than authority: 'In questions of science the authority of a thousand is not worth the humble reasoning of a single individual.'⁴²

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.⁴³ 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 be 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'.⁴⁴ It is denied that 'reality' offers us an objective point of reference to decide on the value of conflicting theories.⁴⁵ Science cannot claim a privileged position, because ultimately even scientific knowledge is just another social construction of reality.⁴⁶ Knowledge and power are regarded to be highly dependent of each other.

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'.⁴⁷ 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:⁴⁸

'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.

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.⁴⁹

'When a regulator makes a decision under uncertainty, there are two possible types of error. The regulator can overregulate a risk [*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 [*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).⁵⁰

The position proposed by Page would, in the case of the EPA, make sense only when (1) over-regulation in terms of public and environmental health would indeed be superior to under-regulation, and (2) that in the face of uncertainty ignoring hormesis is the 'safe' option.⁵¹ 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. In terms of the over-regulatory bias, the choice to ignore hormesis seems logical and very much in line with precautionary culture.⁵² 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 rationale.

Thus it is all the more interesting to review the principal position of the EPA to ignore the biphasic response. In the Belle Newsletter of March 2004, Griffiths –in his response to Hammitt- gives some insight in the (public) reluctance towards hormesis, which is in line with what we have put forward on precautionary culture:⁵³

'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.

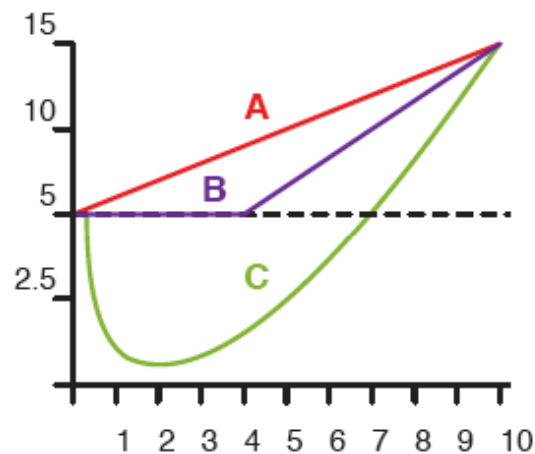
We therefore need to take a closer look at the hormesis issue incrementally from the molecular up to the epidemiological, in which fundamental toxicological, economic and public health issues are interconnected. In our view this would contribute considerably to a more rational approach of chemicals regulation, which shows to have an over-regulatory track record.⁵⁴ We assume –with

Calabrese and Baldwin- that the most fundamental shape of the dose-response curve is neither threshold nor linear, but U-shaped.⁵⁵ We will however address the status of hormesis in relation to the issue of uncertainty and the choice of default models in the regulatory field.

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-cancer' 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).⁵⁶

Figure 1 Three toxicological models



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.⁵⁷ 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 period. 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.

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.⁵⁸ 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 prod 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.⁵⁹

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.⁶⁰

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.⁶¹ 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.⁶² 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.⁶³ So, the straightforward beneficial – adverse dichotomy is not implied per se by the term hormesis.

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.⁶⁴ 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 heme proteins.⁶⁵ 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.⁶⁶ 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.⁶⁷ 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.⁶⁸ These experiments were performed reluctantly, because it is known that SOD1 generates hydroxyl radicals when it is incubated with hydrogen peroxide.⁶⁹ 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.⁷⁰ 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.⁷¹ A prominent flavonoid is quercetin, a good inhibitor of the reactive oxygen species-induced lipid peroxidation.⁷² 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.⁷³ 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:⁷⁴

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 rationalised by means of broadening the view 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.⁷⁵ On May the 7th, 2002, Environment Commissioner Wallström and Enterprise Commissioner Liikaanen 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.⁷⁶ 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.⁷⁷ It also reflects a deep belief in the kind of technocratic social engineering endorsed by the Club of Rome in its report 'The Limits to Growth'.⁷⁸ 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.⁷⁹ 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.⁸⁰ 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.⁸¹

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.⁸² 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.⁸³ 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.⁸⁴ 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 rationale. 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. Government 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. This prerequisite has however very little to do 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.⁸⁵ 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 as an industrial-influenced, self-serving scheme that could lead to less costly, less protective clean-up standards with a much higher cost-effectiveness, especially in relation to public health.⁸⁶

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 foodstuffs of animal origin.⁸⁷ 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 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 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.⁸⁸

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.⁸⁹ 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.⁹⁰

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.⁹¹

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.⁹² 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 unlawful⁹³). 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,⁹⁴ 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 equipment 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.⁹⁵ 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.

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 default safety approach that points in the direction of the widely used linear toxicological models. 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.⁹⁶ Apart from the fact that scientific evidence does show thorough support of the concept of hormesis, 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 the argument against hormesis.

It would 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. The

only sensible approach is to employ the best scientific insights of relevant risks and to adopt sensible assumptions in the face of inexorable uncertainty. Indeed, any reference to the public debate –such as done by Griffiths- in relation to the reluctance to accept hormesis would unwillingly 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. Our contention is that the concept of hormesis needs to be further developed 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. The concept of hormesis shows that the search for safety is not a quest by means of linear extrapolation defaults, despite the EPA's 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 en still is 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.⁹⁷ This is important, as the target of food safety or chemicals regulation is life saving potential (or health protecting potential).

A first step towards regulatory development in light of the concept of hormesis would be to recognise that there are thresholds of toxicological concern. We therefore propose a TIE –a Toxicologically Insignificant Exposure level- for chemical substances.⁹⁸ 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 thereby 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.

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. 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 current regulatory witchhunt of synthetic chemicals amounts to superstition disguised as risk predictions of formalistically correct mathematical formulas devoid of biological meaning and above all ignores the health benefits of homeostatic exercise,⁹⁹ which as the oxygen example shows, is an integral part of life itself. 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.

References

- ¹ U.S. Environmental Protection Agency, *An Examination of EPA Risk Assessment Principles and Practices*. Staff Paper Prepared for the U.S. Environmental Protection Agency by members of the Risk Assessment Task Force, **2004**, EPA/100/B-04/001 (added italics).
- ² Pieterman, R.; Hanekamp, J.C. *The Cautious Society? An Essay on the Rise of the Precautionary Culture*, **2002**, HAN, Zoetermeer.
- Hanekamp, J.C.; Vera-Navas, G.; Verstegen, S.W. *The historical roots of precautionary thinking: the cultural ecological critique and 'The Limits to Growth'*. *Journal of Risk Research*, **2004**, accepted for publication.
- ³ Ulrich B. *Risikogesellschaft: Auf dem Weg in eine andere Moderne*. **1986**, Suhrkamp, Frankfurt am Main.
- ⁴ See also: Giddens, A. (1990) *The consequences of modernity*. Polity Press, Cambridge.
- ⁵ Fukuyama, F. *Trust: The Social Virtues and the Creation of Prosperity*. **1995**, Hamish Hamilton, London.
- Elchardus, M.; Smits, W. *Anatomie en oorzaken van het wantrouwen*. **2002**, VUB Press, Brussels. [*Anatomy and causes of distrust.*]
- See also on the issue of risk: Flynn, J.; Slovic, P. Kunreuther, H. *Risk, Media and Stigma. Understanding Public Challenge to Modern Science and Technology*. **2001**, Earthscan Publications Ltd, London.
- See for an insightful article on knowledge and trust: Sjöberg, L. *Limits of Knowledge and the Limited Importance of Trust*. *Risk Analysis*, **2001**, 21(1), 189 – 198.
- ⁶ Unger, R.M. *Knowledge & Politics*. **1975**, The Free Press, New York.
- Unger, R.M. *Law in modern society: toward a criticism of social theory*. **1976**, The Free Press, New York.
- ⁷ Douglas, M.; Wildavsky, A. *Risk and Culture. An Essay on the Selection of Technological and Environmental Dangers*. **1982**, Berkely University of California Press.
- Furedi, F. *Culture of Fear. Risk-taking and the morality of low expectation*. **2002**, Continuum, London.
- ⁸ Dahrendorf, R. *Class and Class Conflict in Industrial Society*, **1959**, Stanford University Press.
- See also Douglas and Wildavsky, note 7.
- ⁹ Friedman, L.M. *A History of American Law*. **1986**, Touchstone, New York.
- ¹⁰ Simon, J. *The State of Humanity*. **1995**, Blackwell Publisher Limited, Oxford.
- ¹¹ See Furedi, note 7.
- ¹² Jacoby, R. *The End of Utopia. Politics and Culture in an Age of Apathy*. **1999**, Basic Books.
- See also note 2.
- ¹³ Ellman, L.M.; Sunstein, C.R. *Hormesis, the Precautionary Principle, and Legal Regulation*. *Belle Newsletter*, **2004**, 12(2), 2 – 12.
- ¹⁴ Cross, F.B. *Paradoxical Perils of the Precautionary Principle*. *Washington and Lee Law Review*, **1996**, 53, 851 – 925.
- Stone, C.D. *Is There a Precautionary Principle?* *Environmental Law Reporter*, **2001**, 10789 – 10799.
- Bergkamp, L. *Understanding the Precautionary Principle, Parts I and II*. *Environmental Liability*, **2002**, pp. 18-30 and pp. 67 – 82.
- Wiener, J.B.; Rogers, M.D. *Comparing Precaution in the United States and Europe*. *Journal of Risk Research*, **2002**, 5(4), 317 – 349.
- Christoforou, T. *The Regulation of Genetically Modified Organisms in the European Union: the Interplay of Science, Law and Politics*. *Common Market Law Review*, **2004**, 41, 637 – 709.
- Da Cruz Vilaça, J.L. *The Precautionary Principle in EC Law*. *European Public Law*, **2004**, 10(2), 369 – 406.
- ¹⁵ See e.g. Goklany, I.M. *The Precautionary Principle. A Critical Appraisal of Environmental Risk Assessment*. **2001**, Cato Institute, Washington D.C.
- Morris, J. (ed) *Rethinking Risk and the Precautionary Principle*. **2000**, Butterworth-Heinemann, Oxford.
- ¹⁶ See e.g. *Niet alle Risico's zijn Gelijk*. *Dutch Health Council*, **1995**, report 1995/06. [*Not all risks are equal.*] *Risico, meer dan een getal*. *Handreiking voor een verdere ontwikkeling van de risicobenadering in het milieubeleid*. *Dutch Health Council*, **1996**, report 1996/03. [*Risk, more than a number. Directives for a further development of a risk approach of environmental policies.*]
- ¹⁷ Graham, J.D. *Decision-analytic refinements of the precautionary principle*. *Journal of Risk Research*, **2001**, 4(2), 127 – 141.
- ¹⁸ See Stone, note 14.
- ¹⁹ Wiener, J.B. *Hormesis and the Radical Moderation of Law*. *Human & Experimental Toxicology*, **2001**, 20(3), 162 – 164 (see also <http://www.belleonline.com/n13v92.html> last visited the 2nd of December 2004).
- ²⁰ See Stone, note 14.

²¹ Bramwell, A. *Ecology in the 20th century, A history*. 1989, Yale University Press, New Haven.
Bramwell, A. *The Fading of the Greens. The Decline of Environmental Politics in the West*. 1994, Yale University Press, New Haven.

²² See note 21.

²³ Bramwell notes on this theme that the premises of political and biological ecology are analogous. She even asserts that the political variant could not have arisen without the biological. Indeed, in a two-volume reference work on ecotoxicology, the definition of ecotoxicology alludes to the interrelatedness of the normative and the scientific in the ecological sciences (Calow, P. *General Principles and Overview*. In Calow, P. (ed), *Handbook of Ecotoxicology. Volume 1*. 1994, Blackwell Science, Oxford, p. 1.):

‘Ecotoxicology is concerned with *protecting* ecological systems from adverse effects by synthetic chemicals. To do this it attempts to *anticipate* where these substances go in the environment [their *fate*] and what ecological effects they have when they get there.’

²⁴ Popper, K.R. *The Open Society and Its Enemies. Volume I & II*. 1971, Princeton University Press, Princeton.
Popper, K.R. *The Poverty of Historicism*. 2002 (reprint), Routledge Classics, London.

²⁵ Wildavsky, A. *Trial and error versus trial without error*. In: *Rethinking Risk and the Precautionary Principle*. Morris, J. (ed.), 2000, Butterworth-Heinemann, Oxford, UK, p. 22 – 45.

Graham, J.D. *Decision-analytic refinements of the precautionary principle*. *Journal of Risk Research*, 2001, 4(2), 127 – 141.

Marchant, G.E. *The precautionary principle: an ‘unprincipled’ approach to biotechnology regulation*. *Journal of Risk Research*, 2001, 4(2), 143 – 157.

Wiener, J.B. *Precaution in a Multi-Risk World*. *Duke Law School Public Law and Legal Theory Working Paper Series*, 2001, Working Paper No. 23.

²⁶ Wildavsky, A. *But is it True? A Citizen’s Guide to Environmental Health and Safety Issues*, 3rd ed., 1997, Harvard University Press, Cambridge.

²⁷ Tengs, T.O.; Adams, M.E.; Pliskin, J.S.; Safran, D.G.; Siegel, J.E.; Weinstein, M.C.; Graham, J.D. *Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness*. *Risk Analysis*, 1995, 15-3, 369 – 389.
R.L. Keeney, *Estimating Fatalities Induced by the Economic Costs of Regulation*. *Journal of Risk and Uncertainty*, 1997, 14, 5 – 23.

Gerdtham, U.-G.; Johannesson, M. *Do Life-Saving Regulations Save Lives? The Journal of Risk and Uncertainty*, 2002, 24(3), 231 – 249.

Kip Viscusi, W.; Aldy, J.E. *The Value of a Statistical Life: A Critical Review of Market Estimates Throughout the World*. *The Journal of Risk & Uncertainty*, 2003, 27(1), 5 – 76.

Morrall III, J.F. *Saving Lives: A Review of the Record*. *The Journal of Risk & Uncertainty*, 2003, 27(3), 221 – 237.

²⁸ Sunstein, C.S. *Beyond the Precautionary Principle*. 2002, John M. Olin Law & Economics Working Paper No. 149 (2nd series), the Law School, University of Chicago.

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?’

Rip, A. *Co-Evolution of Science, Technology and Society*. 2002, An Expert Review for the Bundesministerium Bildung und Forschung’s Förderinitiative *Politik, Wissenschaft und Gesellschaft* (Science Policy Studies), as managed by the Berlin-Brandenburgische Akademie der Wissenschaften.

²⁹ Douma, W.Th. *The Precautionary Principle. Its Application in International, European and Dutch Law*. 2003, PhD thesis, University of Groningen, the Netherlands.

³⁰ See, Hanekamp, Verstegen, and Vera-Navas, note 2.

³¹ See note 21.

³² Ames, B.; Gold, L.S. *Paracelsus to parascience: the environmental cancer distraction*. *Mutation Research*, 2000, 447, 3 – 13.

Bergkamp, L.; Hanekamp, J.C. *The Draft REACH Regime: Costs and Benefits of Precautionary Chemical Regulation. Environmental Liability*, **2003**, 5, 167 – 180.

³³ World Health Organization, *Dealing with uncertainty – how can the precautionary principle help protect the future of our children?* **2004**, Fourth Ministerial Conference on Environment and Health, Budapest, Hungary, 23 – 25 June 2004.

³⁴ World Health Organization, *Inheriting the World. The Atlas of Children's Health and the Environment*. **2004**, Myriad Editions Limited, Brighton.

Hanekamp, J.C.; Morris, J. *Whose Health Organisation? The Wall Street Journal*, **2004**.

³⁵ *Antimicrobial growth promoting substances: a scientific evaluation of the report of the Health Council of the Netherlands: Committee on antimicrobial growth promoters*. **1998**, TNO Nutrition and Food Research Institute, TNO report V 98.1204.

³⁶ Swann, M.M. *Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*. **1969**, HM Stationary Office, London.

Aarestrup, F. M.; Bager, F.; Jensen, N. E.; Madsen, M.; Meyling, A.; Wegener, H.C. *Surveillance of antimicrobial resistance in bacteria isolated from food animals to antimicrobial growth promoters and related therapeutic agents in Denmark*. **1998**, *APMIS* 106, 606 – 622.

³⁷ Bezoen, A.; Van Haren, W.; Hanekamp, J.C. *Emergence of a Debate: AGPs and Public Health. Human Health and Antibiotic Growth Promoters: Reassessing the Risk. HAN*, **1999**, Amsterdam.

A quite recent publication on virginiamycin and the health-benefits of banning its use in chicken presents the following figures:

'The model shows that the theoretical statistical human health benefits of a VM ban range from zero to less than one statistical life saved in both Australia and the United States over the next five years and are rapidly decreasing.'

Cox Jr., L.A. Popken, D.A. *Quantifying Human Health Risks from Virginiamycin Used in Chickens. Risk Analysis*, **2004**, 24(1), 271 – 288.

³⁸ The Scientific Committee on Animal Nutrition, the official scientific advisers to the European institutions, which reported that the evidence said to justify a ban was not convincing.

See on virginiamycin the SCAN report: *Opinion of the scientific committee for animal nutrition on the immediate and longer-term risk to the value of Streptogramins in Human Medicine posed by the use of Virginiamycin as an animal growth promoter (produced at the request of the Commission in response to the action taken by Denmark under a safeguard clause to ban virginiamycin as feed additive)*. **1998**, SCAN. SCAN concluded the following on streptogramins and vancomycin:

'... 1. no new evidence has been provided to substantiate the transfer of a streptogramins or vancomycin resistance from organisms of animal origin to those resident in the human digestive tract and so compromise the future use of therapeutics in human medicine

2. the development of vancomycin resistance amongst *E. faecium* and methicillin-resistant strains of *Staphylococcus aureus*, ..., are evidently a cause for concern. However, the data provided in the Danish report does not justify the immediate action taken by Denmark to preserve streptogramins as therapeutic agents of last resort in humans.

3. as survey data ... failed to detect a single case of VRE, as Denmark has amongst the lowest incidence of MRSA in Europe and North America, and as coagulase-negative staphylococci remain sensitive to vancomycin, there are no clinical reasons to require the introduction of streptogramins as human therapeutics in Denmark now or in the immediate future. ...'

³⁹ The full text of the ruling (case T13/99 *Pfizer Animal Health SA*) may be found on the website of the European Courts: <http://curia.eu.int/> (last visited on the 2nd of December 2004).

⁴⁰ *Judgments of the Court of First Instance in Cases T-13/99 and T-70/99 Pfizer Animal Health SA v. Council and Alpharma Inc. v Council*. **2002**, Press release No 71/02.

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- ⁴¹ Casewell, M.; Christian Friis, C.; Marco, E.; Paul McMullin, P.; Phillips, I. *The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. Journal of Antimicrobial Chemotherapy*, **2003**, 52, 159 – 161.
- Phillips, I.; Casewell, M.; Cox, T.; De Groot, B.; Friis, C.; Jones, R.; Nightingale, C.; Preston, R.; Waddell, J. *Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. Journal of Antimicrobial Chemotherapy*, **2004**, 53(1), 28 – 52.
- ⁴² Galilei, G. as cited in: *The World of Physics. A Small Library of the Literature of Physics from Antiquity to the Present. Volume I. The Aristotelian Cosmos and the Newtonian System*. **1987**, Simon and Schuster, p. 455.
- ⁴³ Rip, A. *Risicocontroverses en verwevenheid van wetenschap en politiek*. In: *Kennis en methode*, **1992**, 16/1, 63 – 80. [Risk controversies and the intertwining of science and politics.]
- Jasanoff, S. *The Songlines of Risk. Environmental Values*, **1999**, 8(2), 135 – 152.
- Pieterman, R. *Culture in the Risk Society. An Essay on the Rise of a Precautionary Culture. Zeitschrift für Rechtssoziologie*, **2001**, 22(2), 145 – 168.
- ⁴⁴ Gellner, E. *Postmodernism, Reason and Religion*. **1992**, Routledge, London, UK.
- E. Gellner, *Reason and Culture. The Historic Role of Rationality and Rationalism*. **1992**, Blackwell Publishers, Oxford.
- ⁴⁵ Westra, L. *Post-normal Science, the Precautionary Principle and the Ethics of Integrity. Foundations of Science*, **1997**, 2, 237 – 262.
- Funtowicz, S. Ravetz, J. *Post-normal Science. Environmental Policy under Conditions of Complexity*. See <http://www.jvds.nl/pns/pns.htm> (last visited on the 2nd of December, 2004).
- ⁴⁶ Searle, J.R. *The construction of social reality*. **1999**, The Free Press, New York.
- Hacking, I. *The social construction of what?* **1999**, Harvard University Press, Cambridge.
- ⁴⁷ Raffensperger, C. and Tickner, J. *Protecting Public Health and the Environment: Implementing the Precautionary Principle*. **1999**, Island Press, Washington DC.
- ⁴⁸ See note 47, p. 1.
- ⁴⁹ Page, T. *A generic view of toxic chemicals and similar risks. Ecology Law Quarterly*, **1978**, 7, 207 – 244.
- ⁵⁰ See note 26.
- ⁵¹ 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 is typical for precautionary culture.
- Axelrod, D.; Burns, K.; Davis, D.; Von Larebeke, N. 'Hormesis' – *An Inappropriate Extrapolation from the Specific to the Universal. International Journal of Environmental Health*, **2004**, 10, 335 – 339.
- ⁵² See e.g. on overregulation: Hanekamp, J.C.; Frapporti, G.; Olieman, K. *Chloramphenicol, food safety and precautionary thinking in Europe. Environmental Liability*, **2003**, 6, 209 – 221.
- ⁵³ Griffiths, C. *Economic Implications of Hormesis in Policy Making. Belle Newsletter*, **2004**, 12(1), 12 – 14 (added italics).
- ⁵⁴ See for a thorough discussion of this issue: Bergkamp and Hanekamp, note 32.
- See also note 27.
- ⁵⁵ Calabrese, E.J.; Baldwin, L.A. *Toxicology Rethinks its Central Belief. Hormesis Demands a Reappraisal of the Way Risks are Assessed. Nature*, **2003**, 421, 691 – 692.
- ⁵⁶ See note 55.
- ⁵⁷ Calabrese, E.J.; Baldwin, L.A. *Hormesis: A Generalizable and Unifying Hypothesis. Critical Reviews in Toxicology*, **2001**, 31(4&5), 353 – 424.
- ⁵⁸ Rozman, K.K.; Doull, J. *Scientific foundations of hormesis. Part 2. Maturation, strengths, limitations, and possible applications in toxicology, pharmacology, and epidemiology. Critical Reviews in Toxicology*, **2003**, 33 (3 & 4), 451 – 462.
- ⁵⁹ Kaiser, J. *Sipping from a Poisoned Chalice. Science*, **2003**, 320, 376 – 378.
- ⁶⁰ Calabrese, E.J. *The Future of Hormesis: Where Do We Go from Here? Critical Reviews in Toxicology*, **2001**, 31(4 & 5), 637 – 648.
- ⁶¹ Peter A. Parsons, P.A. *Metabolic Efficiency in Response to Environmental Agents Predicts Hormesis and Invalidates the Linear No-Threshold Premise: Ionizing Radiation as a Case Study. Critical Reviews in Toxicology*, **2003**, 33(3&4), 443 – 449.

-
- Liu, S.-Z. *On Radiation Hormesis Expressed in the Immune System. Critical Reviews in Toxicology*, **2003**, 33(3&4), 431 – 441.
- Calabrese, E.J.; Baldwin, L.A. *Inorganics and Hormesis. Critical Reviews in Toxicology*, **2003**, 33(3&4), 215 – 304.
- Calabrese, E.J.; Baldwin, L.A. *Peptides and Hormesis. Critical Reviews in Toxicology*, **2003**, 33(3&4), 355 – 405.
- Calabrese, E.J.; Baldwin, L.A. *Ethanol and Hormesis. Critical Reviews in Toxicology*, **2003**, 33(3&4), 407 – 424.
- Calabrese, E.J.; Baldwin, L.A. *The Hormetic Dose-Response Model is more Common than the Threshold Model in Toxicology. Toxicological Sciences*, **2003**, 71, 246 – 250.
- Chen, W.L.; Luan, Y.C.; Shieh, M.C.; Chen, S.T.; Kung, H.T.; Soong, K.L.; Yeh, Y.C.; Chou, T.S.; Mong, S.H.; Wu, J.T.; Sun, C.P.; Deng, W.P.; Wu, M.F.; Shen, M.L. *Is Chronic Radiation an Effective Prophylaxis Against Cancer? Journal of American Physicians and Surgeons*, **2004**, 9(1), 6 – 10.
- ⁶² See note 59.
- ⁶³ See note 55.
- See also Calabrese, E.J.; Baldwin, L.A. *Chemotherapeutics and Hormesis. Critical Reviews in Toxicology*, **2003**, 33(3&4), 305 – 353.
- ⁶⁴ 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 toxic agent- shows that organisms have substantial adaptation capabilities.
- ⁶⁵ Wickramashighe R.H.; Vilee, C.A. *Early role during chemical evolution for cytochrome P450 in oxygen detoxification. Nature*, **1975**, 256, 509 – 510.
- ⁶⁶ Bast A. *Is formation of reactive oxygen by cytochrome P-450 perilous and predictable? Trends in Pharmacological Sciences*, **1986**, 7, 266 – 270.
- ⁶⁷ Repine J.E.; Bast A.; Lankhorst, I.L.M. *Oxidative stress in COPD. American Journal of Respiratory Critical Care Medicine*, **1997**, 156, 341 – 358 (on behalf of the international oxidative stress study club).
- ⁶⁸ Den Hartog, G.J.M.; Haenen, G.R.M.M.; Boven, E.; Van der Vijgh, W.J.F.; Bast, A. *Lecithinized copper,zinc-superoxide dismutase as a protector against doxorubicin-induced cardiotoxicity in mice. Toxicology and Applied Pharmacology*, **2004**, 194, 180 – 188.
- ⁶⁹ Yim, M.B.; Chock, P.B.; Stadtman, E.R. *Copper zinc superoxide dismutase catalyzes hydroxyl radical production from hydrogen peroxide. Proceedings of the National Academy of Sciences USA*, **1990**, 87, 5006 – 5010.
- ⁷⁰ Den Hartog G.J.M.; Haenen, G.R.M.M.; Vegt, E.; Van der Vijgh, W.J.F.; Bast, A. *Superoxide dismutase: The balance between prevention and induction of oxidative damage. Chemico-Biological Interactions*, **2003**, 145, 33 – 39.
- ⁷¹ Van Acker, S.A.B.E.; Van den Berg, D.-J.; Tromp, M.N.J.L.; Griffioen, D.H.; Van Bennekom, W.P.; Van der Vijgh, W.J.F.; Bast, A. *Structural aspects of antioxidant activity of flavonoids. Free Radical Biology and Medicine*, **1996**, 20, 331 – 342.
- ⁷² Boots, A.W.; Kubben, N.; Haenen, G.R.M.M.; Bast, A. *Oxidized quercetin reacts with thiols rather than with ascorbate: implication for quercetin supplementation. Biochemical and Biophysical Research Communications*, **2003**, 308, 560 – 565.
- ⁷³ Finkel, T.; Holbrook, N.J. *Oxidants, oxidative stress and the biology of ageing. Nature*, **2000**, 408, 239 – 247.
- ⁷⁴ Stebbing, A.R.D. *A Mechanism for Hormesis – A Problem in the Wrong Discipline. Critical Reviews in Toxicology*, **2003**, 33(3&4), 463 – 467.
- ⁷⁵ See Bergkamp and Hanekamp, note 32.
- ⁷⁶ REACH's justification creates a contradiction: government failure calls in the view of the European Commission for more government action.
- ⁷⁷ Carson, R. *Silent Spring*. **1962**, Penguin, Harmondsworth.
- ⁷⁸ See Hanekamp, Verstegen, and Vera-Navas, note 2.
- ⁷⁹ 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.
- ⁸⁰ See note 51 and note 2.

⁸¹ See note 34 and 52.

⁸² See note 74.

⁸³ See note 13.

⁸⁴ Doll, R.; Peto, R. *The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today*. *Journal of the National Cancer Institute*, **1981**, *66*, 1192 – 1308.

Ames, B.N.; Gold, L.S.; Shigenaga, M.K. *Cancer prevention, rodent high-dose cancer tests and risk assessment*, *Risk Analysis*, **1996**, *16*, 613 – 617.

Ames, B.N.; Gold, L.S. *Environmental Pollution, Pesticides, and the Prevention of Cancer: Misconceptions*. *FASEB Journal*, **1997**, *11*, 1041 – 1052.

⁸⁵ See note 55.

⁸⁶ See note 51 and note 2.

⁸⁷ Council Regulation (EEC) No. 2377/90 of 26 June 1990 laying down a Community procedure to set up maximum residue limits of veterinary medicinal products in foodstuffs of animal origin, *Official Journal L224*, **1990**, 18 August, 1 – 8.

⁸⁸ IPCS-INCHEM (Chemical Safety Information from Intergovernmental Organizations), webpage <http://www.inchem.org/documents/jecfa/jecmono/v23je02.htm> (last visited on the 2nd of December 2004).

⁸⁹ IPCS-INCHEM (Chemical Safety Information from Intergovernmental Organisations), webpage <http://www.inchem.org/documents/jecfa/jecmono/v33je03.htm> (last visited on the 2nd of December 2004).

⁹⁰ See on the risks of ophthalmic use of CAP: Laporte, J.R.; Vidal, X.; Ballarin, E.; Ibanez, L. *Possible association between ocular chloramphenicol and aplastic anaemia – the absolute risk is very low*. *British Journal of Clinical Pharmacology*, **1998**, *46*(2), 181 – 184.

⁹¹ Janssen, P.A.H.; Baars, A.J.; Pieters, M.N. *Advies met betrekking tot chlooramfenicol in garnalen*. RIVM/CSR, **2001**, Bilthoven, The Netherlands. [*Recommendations on chloramphenicol in shrimp*.]

⁹² See note 74.

⁹³ Policies aimed at the exclusion of risk or that generate an impossible burden on economic parties in terms of proof of no-harm is regarded as unlawful as is discussed in the Pfizer verdict by the *Court of First Instance* (Case T13/99 *Pfizer Animal Health SA*, paragraph 130; see note 39):

'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 *probatio 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.'

⁹⁴ See note 27.

⁹⁵ Hanekamp, J.C. Wijnands, R.J. *Analytical technology, risk analysis and residues of veterinary substances: A précis and a proposal for coherent and logical clinical residue legislation*. *Joint FAO-WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL (Bangkok, Thailand 24-26 August 2004)*, **2004**, working document.

See also Hanekamp, J.C.; Kwakman, J. *Beyond zero tolerance: a new approach to food safety and residues of pharmacological active substances in foodstuffs of animal origin*. *Environmental Liability*, **2004**, *1*, 33 – 39.

⁹⁶ See note 51.

⁹⁷ See note 27.

⁹⁸ Rulis, A.M. *Threshold of regulation: Options for handling minimal risk situations*. In: *Food Safety Assessment*. **1992**, ACS Symposium Series 484, 132 – 139.

Carcinogens and Anticarcinogens in the Human Diet. A Comparison of Naturally Occurring and Synthetic Substances. Committee on Comparative Toxicity of Naturally Occurring Carcinogens, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, **1996**, National Academy Press, Washington D.C.

⁹⁹ As paraphrased from Rozman and Doul, note 58.