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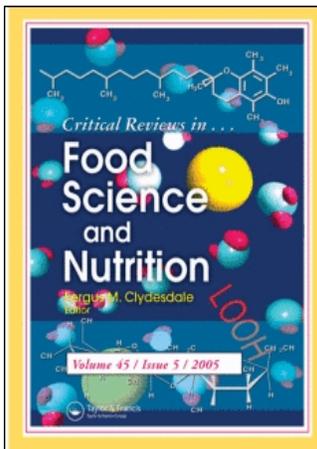
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# Food Supplements and European Regulation within a Precautionary Context: A Critique and Implications for Nutritional, Toxicological and Regulatory Consistency

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*In this paper, we review European legislation in the field of micronutrient food supplements and find it wanting. It is shown that the precautionary principle, embedded in European food legislation, pre-empts innovative developments in this field. In view of the scientific advances in micronutrients research, we subsequently critique the precautionary perspective and propose a novel outlook on micronutrients food supplements regulation. However, this requires a transition from the “survival” approach of the current deficiency-related RDAs to a “health-optimization” approach of a n(ew)-RDA. Genomic integrity is central in this envisioned transition.*

**Keywords** Micronutrients, food supplements, European regulation, precautionary principle, regulatory innovation, Intended Normal Use (INU)

## INTRODUCTION

Food is essential to the maintenance, development, functioning, and reproduction of human life. During his or her lifetime an individual consumes, on average, 30 tons of food, in seemingly endless dietary varieties. However, digestion splits all the foods found in all these different diets into the same basic nutrients.<sup>1</sup>

Food, therefore, is chemistry, and the mixture of chemicals that food represents can be divided into four basic categories: nutrients, non-nutritive naturally occurring components (including antinutritives<sup>2</sup> and natural toxins), man-made contaminants and additives. The nutrients account for more than 99.9% of the food content. The main classes of nutrients are carbohydrates, proteins, fats, and vitamins, and minerals. The former three constituents of food are called macronutrients and are the major sources of energy and building materials for humans. The latter are called micronutrients, as these are only required in rela-

tively small amounts. Micronutrients differ from other chemical substances in foods in that they are essential for the human physiology, so that different adverse (toxicological) effects can result from intakes that are *too low* (the typical deficiency diseases) as well as *too high*. Food products as a whole are estimated to consist of many hundreds of thousands of different chemicals. All these food-content chemicals have their own specific pharmaco-toxicological profile, both individually and interactively (synergism and antagonism).

A combined risk profile of food has to include not only the chemistry as outlined above, but also food microbiology and dietary habits. Although food microbiology is not part of the discussion here, the entirety of these issues results in the following relative importance of actual food hazards<sup>3</sup> (Table 1).

Dietary imbalance is a high-risk aspect of food consumption, on par with microbial contamination, since repetitive and limited diets increase the risk of deficiencies (resulting in acute (scurvy in the case of lack of vitamin C) and chronic diseases) and chronically expose humans to the same detrimental loads (by load we simply refer to the total intake of certain bio-available

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**Table 1**

Ranking	Issue	Relative risk
1	Microbiological contamination	100 000
2	Nutritional imbalance	100 000
3	Environmental contaminants, pollutants	100
4	Natural toxins	100
5	Pesticides residues	1
6	Food additives	1

food-endogenous chemical compounds, resulting in a certain concentration within the organism) of non-nutritives over longer periods of time. The relationship between diet and disease (especially cancer) has most notably been discussed by the Doll and Peto paper on the causes of cancer.<sup>4</sup> Their estimate, made in 1981, was that unbalanced diets account for approximately one-third (35%) of cancer risk (keeping in mind the range of estimates of 10–70%). Later estimates are in accord with this approximation.<sup>5</sup>

Historically, diet and cancer have been viewed and researched in terms of exposure to potential carcinogens, such as polyaromatic carbohydrates or heterocyclic amines, but also alcohol (ethanol). However, the presence of carcinogens (and anticarcinogens for that matter<sup>6</sup> in the human diet is ubiquitous in unprocessed as well as in industrially processed and home-prepared foods. Plants in nature—including those plants that are part of the human diet—synthesise toxic chemicals in profuse amounts, apparently as a primary defence mechanism against predatory organisms such as bacteria, fungi, and insects.<sup>7</sup>

Therefore, in order to explicate the diet-related cancer incidence, an increasing number of scientific research and concomitant publications focus instead on the micronutrient status of humans in relation to *long-term disease incidence* such as cancer, cardio-vascular diseases and aging as opposed to on the one hand the presence of carcinogens (natural or synthetic) in food and its effects on health, and on the other hand prevention of deficiency diseases.<sup>8</sup> These research findings mirror the Doll and Peto estimate that dietary imbalance is one of the major risk factors in relation to food consumption.

Additionally, there is increasing scientific evidence that apart from the common essential micronutrients, there are many constituents of edible plants as part of the human diet, which may well support health. Obviously, these compounds, as well as the common vitamins and minerals, are not found in food for the benefit of human health, but are a contingent (fortuitous) part of food products. The best researched of these bioactive plant compounds—polyphenols (sometimes referred to as vitamin P)—may either help to prevent disease or may act as disease-inhibitors at an early disease stage.<sup>9</sup> This chemical group as a whole has a wide range of biological effects including antioxidant, anti-mutagenic and anti-inflammatory properties that indicate long-term benefits and *mutatis mutandis* long-term risks when humans consume these compounds below a certain level. Although these compounds are usually not classified as micronutrients, and no classical deficiency symptoms may be observed, as is normally the case with vitamins and minerals, consump-

tion may be advantageous in terms of long-term benefits (e. g. in relation to the incidence of cancer). We will therefore in this review take account of plant-derived bioactive compounds (such as polyphenols) within the food area and in some measure build on recent work done in this field.<sup>10</sup>

As a primary consequence of the increasing focus on long-term health issues in relation to (micro)nutrient food compounds, it seems essential to go beyond the standard micronutrients RDA-methodology, which centers on common vitamins and minerals and deficiency-prevention rather than on long-term benefits, and—in our view incorrectly—excludes other (micro)nutrient food compounds. For that reason, in this review we will use the term micronutrients for more (micro)nutrient food compounds than just these vitamins and minerals. In the Food Supplements Directive 2002/46/EC, these are referred to as “other substances.”

Nowadays there is a growing market for food (supplemental) products with perceived and real health benefits. This development, combined with the consumers’ general *and* mistaken perception that “natural equals safe” or “natural equals healthy,” results in a tendency for increased use of food supplemental micronutrients but also botanical products both as bioactive ingredients in food supplements and herbal teas. Nevertheless, a long history of use does not as such “guarantee safety” (obviously a contradiction in terms; see below); botanical preparations e. g. may contain individual ingredients known to be genotoxic and carcinogenic.<sup>11</sup> Consequently, the Food Supplements Directive was implemented in order to safeguard human health in view of the potential toxicity of excess intake of micronutrient food supplements that have become increasingly available and are consumed in increasing amounts.

### **THE EUROPEAN FOOD SUPPLEMENTS DIRECTIVE**

The European Food Supplements Directive concerns food supplements marketed as foodstuffs and presented as such for the purpose of supplementing the human diet.<sup>12</sup> We define food supplements, in accordance with the Directive, as concentrated sources of micronutrients or other substances with a nutritional or physiological effect, embodied in capsules, tablets, pastilles, and other similar forms of embodiment, such as sachets, ampoules, and dispensing bottles to provide controlled dosages of liquids and powders containing micronutrients, irrespective of their ways of manufacturing. Some micronutrients are being isolated or extracted from natural materials; others are being produced by way of fermentation or chemical synthesis. By definition, food supplements are marketable finished products that are explicitly presented to the public for supplementation of the diet. Food supplements cannot be presented as medicines or as a substitute for medicines. Food supplements may or may not exceed the intake of micronutrients present in the consumed diet.

The Food Supplements Directive does not apply to medicinal products as defined by Directive 2001/83/EC.<sup>13</sup> Medicinal products are defined as any substance or combination of substances

presented for treating or preventing, or making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings. Botanical products derived from (edible) plants—as products that enjoy increasing public and regulatory attention—are usually regarded as medicinal in character, although some products are close or even identical to food while others indeed come close to or are in fact medicines.<sup>14</sup>

A number of ground-rules and ordering principles have been formulated in relation to food supplements:<sup>15</sup>

- (i) a high level of consumer protection (in part based on the precautionary principle)
- (ii) food ubiquity and availability;
- (iii) Safe Upper Limits (SULs) through conventional risk assessment methodology and the development of Maximum Permitted Levels;
- (iv) reference average dietary intake;
- (v) risk assessment prior to market entrance of micronutrients not yet listed on Positive Lists;
- (vi) ways of presenting micronutrient food supplements to the public (labelling and health claims).

The Directive in large part is based on what we describe as the “assessment paradigm”: through scientific research, toxicological risks of excess intake of food-derived micronutrients are elucidated. Based on these research results, European regulatory risk management strategies are formulated and implemented. The “logic to regulate” once toxicology elucidates a certain risk is, however, occasioned by numerous and usually implicit value-judgments we will address further below.

The English Expert Group on Vitamins and Minerals (EVM) has in 2003 produced a report in which a normative methodology is developed and described for vitamins and minerals.<sup>16</sup> The normative concept produced by the committee—as said—is the SUL, which is described by the committee as “the determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provides a framework within which the consumer can make an informed decision about intake, having confidence that harm should not ensue.”<sup>17</sup> Below we will describe and discuss the toxicological foundations of this normative framework.

On account of a number of German studies, a difference of opinion has evolved around the English SULs.<sup>18</sup> The reports “Verwendung von Vitaminen in Lebensmitteln” and “Verwendung von Mineralstoffen in Lebensmitteln”—compiled by the German Federal Institute for Risk Assessment (BfR)—propose structurally and significantly lower recommended maximum permitted levels than those reported in the UK EVM study.<sup>19</sup> Both major reviews choose a similar approach in their respective studies more or less derived from a physiology and/or standardized (average) diet exposure combined with toxicological data and conventional modelling. Nevertheless, the conclusions vary noticeably. For example, the BfR’s report proposes a 225 mg

maximum for vitamin C (EVM—1000 mg), a 5.4 mg maximum for B6 (EVM—10 mg), and 9  $\mu$ g for B12 (EVM—no maximum).

The above-mentioned ground-rules and principles carry distinct overtones of precaution focussed on the risk of excess intake of micronutrient food supplements, whereby the Directive has a regulatory preoccupation with market failure.<sup>20</sup> Supplement food compounds, including those that have been legitimately marketed in one or more Member States in accordance with the relevant national regulations, will now only be placed on EC’s Positive List(s), when an appropriate (characterized by us as precautionary) scientific risk characterization is performed and presented. Whether or not micronutrient supplement intake might add to the overall health of European citizens is, from a regulatory point of view, regarded as irrelevant. These issues characterize one part of the underlying values of the Directive.

The Food Supplements Directive takes an (over)regulatory excess toxicity outlook directed at avoiding false-negatives. This position is asymmetric and typical for precautionary culture: it assumes what actually should be proven, namely, that the health effects of an assumptive over-regulatory approach at avoiding false-negatives would be superior to the alternatives. The concomitant assumption is that there are no health detriments from proposed (over)regulation. Something (health) is gained with nothing lost (no adverse health effects from over-regulations).<sup>21</sup> The Food Supplements Directive clearly chooses not to underestimate risk through focussing on excess toxicity, in order to protect public health. The burden of proof of safety subsequently lies with the marketing parties. The issues mentioned here represent another part of the underlying values of the Directive.

## CONTEXT AND CRITIQUE

We will propose here an outline for a straightforward, transparent, and coherent benchmark methodology to regulate micronutrient food supplements cost-effectively within a European (or even a global) level-playing field in which assessment and management—facts and values—are explicitly linked. Food supplements should be allowed on market taking into consideration the issues of safety, risks, costs, and benefits. The perspective we choose in relation to any type of (newly discovered) micronutrient, is the actual “mandatory” amount of micronutrients for the human organism that maximizes a healthy lifespan (which, parenthetically, in a number of cases appears to be higher than the amount needed to prevent acute deficiency disease<sup>22</sup>; see as below), as opposed to the customary nutritional approach of either classical deficiency or to the customary regulatory approach of the prevention of excess toxicity.

The above-described approach requires more than the assessment paradigm can provide for. As Cramer, Ford and Hall already remarked in 1978 in their seminal paper on the “assessment paradigm,” which in fact highlights some of the values entertained by the Food Supplements Directive:

“Safety evaluation is caught in a frustrating circle. It is neither possible nor sensible to try to obtain the information needed to assess every imaginable toxic risk associated with every substance, and pursuit of greater safety therefore demands the setting of priorities as well as sensible limits for investigation. To do this with confidence requires possessing the very information that is lacking and that can be won only slowly on a few substances at a time, with significant uncertainty and at considerable cost. This requires priorities, and completes the circle of frustration.”<sup>23</sup>

In other words: unremitting assessment of increasing numbers of micronutrients (or other chemicals for that matter) that will come to market, in part as the result of increasing knowledge of the health impact of all sorts of food-endogenous chemicals, will prove to be prohibitive in terms of restricted research and government facilities and (human and financial) resources, scientific and public interests, and etceteras.

More importantly, and this is rarely grasped in full substance, many of the issues which arise in the course of the interaction between science (or technology) and society—e.g. the beneficial or deleterious side effects of technology *in casu* micronutrient food supplementation—hang on the answers to questions which can be asked of science and yet which cannot be answered by science. Weinberg coined these issues as trans-scientific.<sup>24</sup> Issues of health and safety can be structured in the language of science, as questions of fact, yet cannot be answered by science; they transcend science. These issues are trans—scientific as they, among other things, refer to value judgments we to some extent described above.<sup>25</sup>

We do not take this to be a shortcoming of science as such, but an overstatement of the possibilities of science, especially in relation to the normative issues of health and safety.<sup>26</sup> Within the field of micronutrients the following value judgments could for instance be stated: How safe is safe-enough?,<sup>27</sup> Focus on risks or benefits of micronutrients?, Focus on market or government failure?,<sup>28</sup> and etceteras. Facts and values, within the specific framework of the justification phase of science, however, need to be separated when analysed, yet taken on board fully in the final analysis.<sup>29</sup> The “logic to regulate” once toxicology elucidates a certain risk is occasioned by numerous and usually implicit value-judgments, which, as said, are not scientific but trans-scientific.

Legitimate policies dealing with “toxicological concerns”, therefore, need to go beyond the “assessment paradigm” in order to properly and explicitly address the implicit value-judgements. Management options derived from the assessment paradigm could well prove to be unworkable and extremely conservative as a result of for instance secondary risk management concerns (reputation and liability),<sup>30</sup> and other precautionary deliberations (see below).<sup>31</sup> What therefore should be incorporated into a food supplements regulation (or any other type of regulation for that matter) is at least a cost-benefit framework:

- (i) how much of
- (ii) what type of regulation generates

- (iii) how much health and/or
- (iv) prevents how much risk with the aid of
- (v) how much scientific research in relation to the consumption of micronutrient food supplements?<sup>32</sup>

Numerous economic analyses show that beyond certain social-economic and governmental expenditures, regulation devised to enhance safety in point of fact establishes the reverse. Increasing social stratification,<sup>33</sup> cost-induced fatalities,<sup>34</sup> or risk trade-offs<sup>35</sup> are three reasons for this to happen. These dilemmas are debated particularly in relation to environmental policies,<sup>36</sup> and might serve as a forewarning to other regulatory fields including food safety regulation.

Subsequently, the question whether food supplements regulation needs to be formulated in an *ex ante* (in advance of introduction to the market through scientific research) or *ex post* (after introduction to the market through monitoring) framework is brought about by this deliberation. The European normative framework of SULs is to be characterized as an *ex ante* approach of the food supplements market, which produces sliding scale dimensions: the stringency of *ex ante* regulation is correlated to the advance timing and tightness of proposed (and implemented) food supplement policies. Regulation is “more precautionary” when it intercedes earlier and/or more rigorously to preclude uncertain future adverse consequences—in terms of excess toxicity solely—of future marketed micronutrient food supplements. The thrust towards *ex ante* regulation is in line with the EU Communication on the precautionary principle.<sup>37</sup> We will discuss the precautionary principle below.

However, as micronutrients cannot be characterized other than by way of a 2-sided benefits-risks profile (an (inverted) U-shaped dose-response curve that marks benefits and risks), the benefits of exposure to micronutrients must be an integral factor in the regulatory equation.<sup>38</sup> In actual fact, European food-safety legislation has as its goal “a high level of protection for human life and health” whereby *mutatis mutandis* the potential benefits side of micronutrients by definition cannot be ignored. Health-related data of micronutrients, however, are routinely not considered: “The Expert Group on Vitamins and Minerals (EVM) is an independent expert advisory committee which was asked to advise on safe levels of intakes of vitamins and minerals in food supplements and fortified foods. . . . Review of nutritional or non-nutritional beneficial effects or non nutritional use in medicines was outside the terms of reference of the group.”<sup>39</sup>

This subsequently begs the question in what way micronutrients are most effectively regulated: *ex ante* or *ex post*? It is *a priori* not self-evident or logical that the regulation of micronutrients food supplements should, in order to serve “a high level of protection for human life and health,” be approached from an *ex ante* focus of risks of excess exposure, as with micronutrients we are also confronted with (potential) benefits at certain intakes. Indeed, the 2-sided deficiency-excess profile of micronutrients results in a double false-positive false-negative conundrum. Overregulation of excess-toxicity (potentially resulting in excess-toxicity false-positives) could result

in underregulation of deficiency (potentially resulting in deficiency false-negatives); conversely overregulation of deficiency (potentially resulting in deficiency false-positives) could result in underregulation of excess-toxicity (potentially resulting in excess-toxicity false-negatives).

### MICRONUTRIENT ASSESSMENT METHODOLOGIES: PRECAUTIONARY ASYMMETRY

The context in which safety assessments of micronutrients are usually carried out is the Deficiency-Excess model. At one end of the model scale, where the levels of exposure decrease, i.e. at increasing levels of deficiency, the organism will suffer increasing harm. At the other end of the scale, where the levels of exposure increase, the organism incurs an increasing risk of a harm that, however, differs from the harm caused at the deficiency-end of the scale. Within the bandwidth of deficiency and toxicity a physiological optimum is assumed (homeostasis), which, however, may vary between different micronutrients and various individuals (intra- and inter-individually) and populations. Below (Figure 1) we depict a generalized model of micronutrient toxicology and the derivation of SULs.

The curve represented here renders an idealized depiction of reality. What is not included in this figure is the time vector. Deficiency or excess diseases are the result of a certain time-frame of under—or overexposure of micronutrients, which might have either short-term or long-term effects.

The RNI (Reference Nutrient Intake, which is similar to the Recommended Daily Allowance (RDA) depicted in the normal distribution curve above the U-shaped micronutrient curve) is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. The Es-

timated Average Requirement (EAR) is the daily nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a group. The Lower Reference Nutrient Intake (LRNI) is daily nutrient intake value, which is adequate for only 2.5% of healthy individuals in a group.<sup>40</sup>

In order to establish a SUL (in the customary toxicology jargon this translates into an Acceptable Daily Intake), the NOAEL (No-Observed Adverse Effect Level) and LOAEL (Lowest-Observed Adverse Effect Level) levels for micronutrient exposure is divided by an uncertainty factor (UF). Safety or uncertainty factors (UFs) are applied to allow for uncertainties in the use of data obtained from human or animal studies in order to establish the amount of a particular substance that can be consumed without harm. Applying UFs to a NOAEL (or LOAEL) will result in a value for the derived UL that is less than the experimentally derived NOAEL. The larger the uncertainty, the larger the UF and the lower the UL, which represents a lower estimate of the threshold, beyond which risks of exposure to the specific micronutrient may increase.

Generally, values for uncertainty factors of 10 for inter-human variations, 10 for animal to human (inter-species) extrapolations, and less than 10 for LOAEL to NOAEL extrapolations (usually 3) are used when dealing with non-carcinogens. These separate factors allow for differences in sensitivity between individuals and between species that may result from differences in, for example, absorption, metabolism, or the biological effect of the substance under consideration. The separate factors are multiplied assuming that they are independent variables; the standard factor between a NOAEL and an ADI is a 100 ( $10 * 10$ ).

The above-described methodology is also used for micronutrients, defended on the basis of the correctly asserted general exposure-related toxicity of any type of chemical, including micronutrients. The EVM report remarks that “the use of more refined values requires data specific to the chemical under

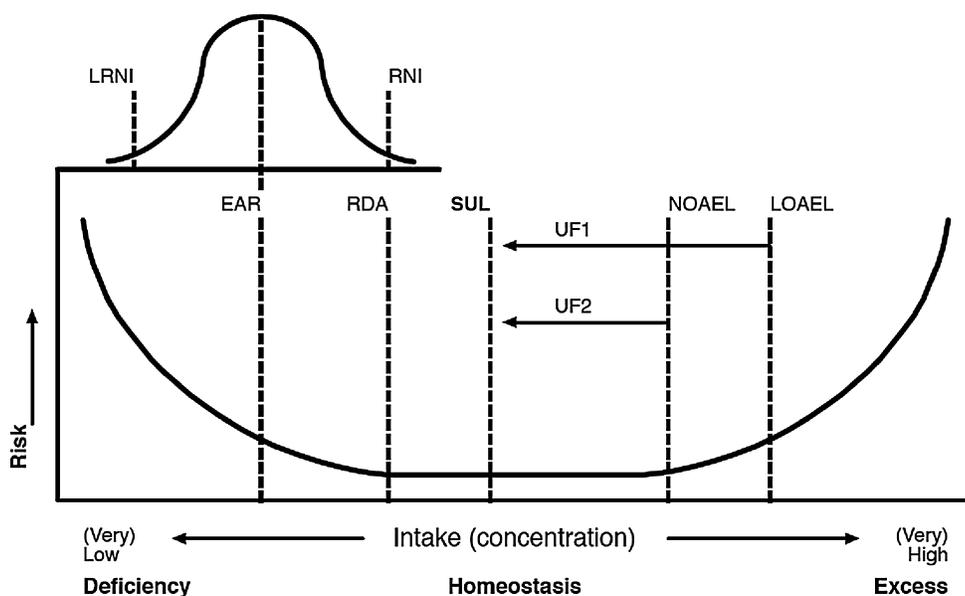


Figure 1 Generalized toxicological model for the determination of SULs for micronutrients

consideration to support the use of a smaller or larger chemical-specific factor.<sup>41</sup> Here it must be remembered, however, that for macronutrients it is not possible to increase the concentrations in the diet of test animals in order to give a margin of exposure of greater than 100 times the human exposure. By and large, this applies also to micronutrients. Accordingly, the paradigm of high-dose animal studies with the application of large UFs—used within the field of food research for e.g. additives—cannot straightforwardly be applied to assess the safety of those micronutrients as such.

The underlying premises of regulatory scientific research into micronutrients are the logical consequences of the predominant philosophy that dictates that matters of health and safety are most easily formulated, researched and implemented from a viewpoint of toxicological risks of excess exposure. Experimentally such an approach is the most accessible option,<sup>42</sup> and sociologically this approach most effectively deals with the secondary risks of policies.<sup>43</sup> Moreover, this philosophy also is in line with the public bias for negative information about possible health risks of products or activities.<sup>44</sup> Recent studies on the role of micronutrients in the maintenance of human health, however, show a more complex nature, that goes beyond deficiency diseases and excess toxicity. In order to make this clear, what is required, first, is a different description of the U-shaped curve so typical of micronutrients.

#### **MICRONUTRIENTS AND GENOMIC INTEGRITY: BEYOND THE RDA**

Even though the European regulatory concern is focussed on excess toxicity, health risks due to micronutrients are habitually related to deficiencies in the diet, and not excess. Dietary excess of micronutrients does not commonly instigate major toxicological problems as minerals and the majority of vitamins are

water-soluble and are readily eliminated by excretion as well as metabolism.<sup>45</sup> As an overarching perspective, micronutrient deficiency is a well-known historic phenomenon societies had to deal with for centuries; a broad range of food products, including and especially fruits and vegetable, have been available to almost all social groups in the Western world only the last couple of decades.

Apart from a lack of micronutrients in the diet, anti-nutritives are known for their induction of deficiencies. Phytic acid forms insoluble salts with many types of heavy metal ions, thereby reducing the bioavailability of quite a few minerals and essential trace elements. Oxalic acid is similarly capable of inducing deficiencies through binding of bivalent cations. Calcium absorption is seriously hindered by oxalic acid. A third group of antinutritives is the so-called glucosinolates. Many glucosinolates are goitrogenic; that is causing an enlargement of the thyroid gland, commonly visible as a swelling of the anterior part of the neck, on account of iodine deficiency. Cabbage goiter—induced by an excessive consumption of cabbage—is the result of the inhibition of iodine uptake by the thyroid gland.<sup>46</sup>

Hypervitaminosis is usually associated with vitamins A and D, which are lipid-soluble. The toxicity of certain foods that contain high amounts of vitamin A has been recognized for centuries. The 1597 diary of Gerrit de Veer, which he wrote while taking refuge in the winter in Nova Zembla during an attempt to reach Indonesia by the northern passage, states that he and his men became critically ill after eating polar-bear liver, but in due course recovered. De Veer's diary also notes extensive and noticeable desquamation (the shedding of the outer layers of the skin) during recovery.<sup>47</sup> Cases of acute vitamin A intoxication have been reported in polar regions after eating copious amounts of polar bear liver, containing 100 000 IU (1 IU equals 0.3 µg retinol)<sup>48</sup> vitamin A per gram of liver.

Below (Figure 2) we have summarized the generalized pharmacological shape of the dose-response curve of essential

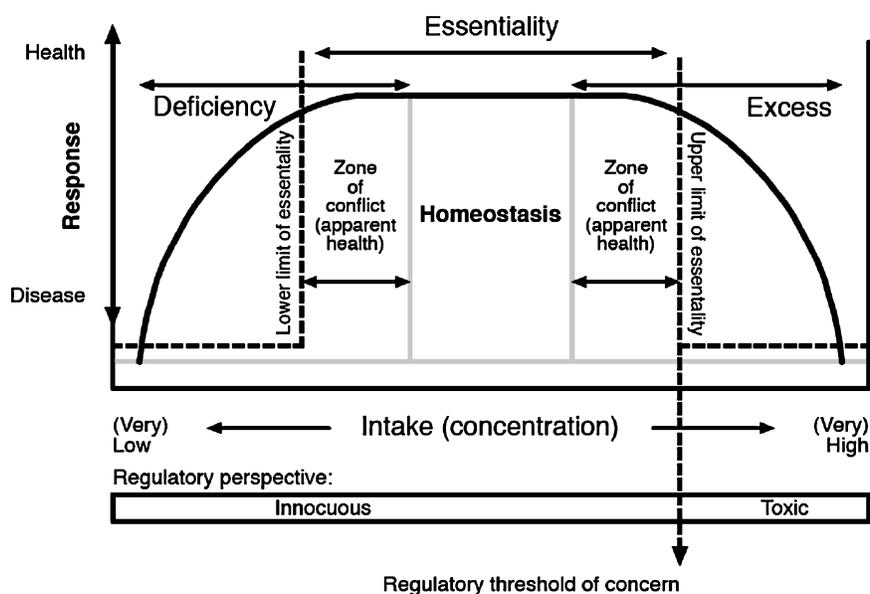


Figure 2 The (inverted) U-shape curve of micronutrients<sup>49</sup>

micronutrients such as vitamins, minerals and other compounds. We present the U-shaped curve in an inverted fashion. The figure does not address deficiency and excess toxicology from a regulatory or experimental point of view but centres on the organism as such as it is exposed across a certain concentration range of micronutrients. For clarity, beneath the curve we have positioned the regulatory concerns in relation to the pharmacological shape of the dose-response curve:

The margin between essentiality (that is, at a minimum, the prevention of deficiency, which also, as is our contention, should refer to long-term effects such as cancer) and excess can range from a few-fold for trace elements such as selenium,<sup>50</sup> to orders of magnitude for some of the B group vitamins such as biotin or pantothenic acid.<sup>51</sup> Current RDAs for micronutrients are based on the prevention of diseases of deficiency: scurvy in the case of vitamin C,<sup>52</sup> rickets in the case of vitamin D.<sup>53</sup>

Numerous papers, however, have addressed the issue of increased intake of fruit and vegetables and cancer incidence, whereby intrinsically or explicitly, the role of micronutrients are addressed.<sup>54</sup> Diets rich in fruits and vegetables are protective against e.g. cardiovascular diseases and cancer.<sup>55</sup> Diet, as a key factor in determining genomic integrity (which we refer to as DNA repair, DNA synthesis and apoptosis, seems more important than previously estimated.<sup>56</sup> Because diseases of development, degenerative diseases and aging itself are partly caused by damage to DNA, it seems logical that we should focus our attention in terms of the RDA on defining optimal requirements of key micronutrient compounds for preventing damage to DNA, rather than focusing on avoiding micronutrient deficiencies.

Indeed, there is increasing evidence that higher levels of many micronutrients may be necessary for various DNA maintenance reactions, and that the current RDAs for some micronutrients may well be inadequate to protect against genomic instability.<sup>57</sup> This could result in an increase in e.g. DNA damage (potentially resulting in cancer), and mitochondrial decay (resulting in among others accelerated ageing and degenerative diseases).<sup>58</sup> The need to set micronutrient requirements to minimize DNA damage instead of avoiding deficiency diseases seems a way forward.<sup>59</sup> In addition, the optimum amount of micronutrients varies with age, constitution—the requirements of the elderly for vitamins and metabolites are likely to be different from those of the young—<sup>60</sup> and with genetic make-up.<sup>61</sup>

Customary micronutrient deficiencies are expected to damage DNA by the same mechanism as radiation. Recently—as a first example—radiation exposure was compared with folate deficiency in order to try to put these risks in perspective.<sup>62</sup> DNA double-strand breaks, the most serious DNA lesion caused by ionizing radiation, are also caused by several vitamin or mineral deficiencies, such as for folate. These findings imply that a diet poor in folate may pose a risk of DNA damage comparable to that of a relatively high dose of radiation. Interest in folate over the past decade has increased considerably, largely because scientists have recognized the importance of this vitamin in treating a broad range of both developmental and degenerative disorders that are sensitive to even marginal deficiencies in B vitamins.<sup>63</sup>

Therefore, the use of folate fortification has great potential benefit, and food fortification with folate is now common in e.g. the US.<sup>64</sup>

A second example concerns selenium. Selenium is an essential element for humans, animals, and some species of microorganisms. The selenium range between excess toxicity and deficiency, as mentioned above, is narrow. Keshan disease, which is an endemic cardiomyopathy in man results from selenium deficiency. (The disease, in which the heart muscle becomes inflamed with loss of function, may have multiple causes including viral infections.<sup>65</sup>) The pathological changes associated with Keshan disease mainly involve serious myocardium degeneration. Keshan disease is endemic in selenium-deficient rural areas of China.<sup>66</sup>

The recommended daily allowance (RDA) is 55  $\mu\text{g}$  Se per day for healthy adults.<sup>67</sup> The smallest possible required selenium dose—research suggests a minimum of 20  $\mu\text{g}/\text{day}$ —is to prevent Keshan disease.<sup>68</sup> However, there is a growing body of evidence suggesting that intake of selenium beyond the RDA bestows further benefits. Evidence for the role of selenium as an anti-carcinogenic agent comes from different scientific fields summarized elsewhere.<sup>69</sup> The “Nutritional Prevention of Cancer (NPC) Trial with Selenium” was the first double-blind, randomized, placebo controlled clinical trial in a western population to observe a reduced incidence of cancer with nutritional supplementation.<sup>70</sup> Supplementation with 200  $\mu\text{g}$  Se/day given to subjects with baseline dietary intakes of around 90  $\mu\text{g}/\text{day}$ , suggest an anticancer effect.<sup>71</sup> Doses above the RDA, therefore, seem to be needed to inhibit genetic damage and subsequently cancer.<sup>72</sup>

A third example comprises polyphenols, such as flavonoids. Unlike micronutrients such as selenium and folate, plant polyphenols are a group of chemicals that may play a beneficial role in human nutrition, but are not regarded as essential for human health. The group as a whole has a wide range of biological effects including antioxidant, anti-mutagenic and anti-inflammatory properties.<sup>73</sup> Polyphenols are the most abundant antioxidants in the diet and are widespread constituents of fruits, vegetables, cereals, dry legumes, chocolate, and beverages, such as tea, coffee, and wine. Apart from vitamins and minerals, polyphenols probably are the widest marketed groups of dietary food supplements. This class of plant chemicals contains until now more than 8000 known compounds.<sup>74</sup> The total dietary intake of polyphenols is roughly estimated to be in the range of 1 g per day, although this intake may differ as a result of varying dietary habits.<sup>75</sup>

Epidemiological studies associating the intake of various polyphenol sources (from e.g. green tea and red wine) have been, in the main, indicative of protection against diseases.<sup>76</sup> Experimental studies on animals and cultured human cell lines corroborate a role of polyphenols in the prevention of cardiovascular diseases, cancers, neurodegenerative diseases, and etceteras.<sup>77</sup> Indeed, there are multiple lines of evidence from different scientific fields supportive of the argument that frequent consumption of for instance green tea is inversely associated with

the risk of chronic human diseases. The chemopreventive and chemoprotective effects of green tea have been largely attributed to anti-oxidative and anti-inflammatory activities of its polyphenolic compounds.<sup>78</sup> Equally, polyphenols from red wine, for instance, inhibit the process of colon carcinogenesis (induced by chemicals) in rodents, and reduce colonic mucosa DNA oxidation.<sup>79</sup> Other research has shown the anti-proliferative effect of resveratrol, a polyphenol present in grapes and wines, on the growth of human colon cancer cells.<sup>80</sup>

Reports of toxicity of polyphenols are limited, as most research in this field, for all sorts of reasons, is focused on benefits. Therefore knowledge of toxicity is restricted. Toxicity should, however, not be disregarded.<sup>81</sup> Cases of acute toxicity have been reported in animals consuming plants rich in tannins.<sup>82</sup> In humans, similar cases of acute toxicity following the consumption of food rich in polyphenols have, until now, not been reported.

Polyphenols consumed in high amounts could have pro-oxidant effects<sup>83</sup> (keeping in mind the issue of bioavailability).<sup>84</sup> Such pro-oxidant have as yet not been demonstrated *in vivo*. Furthermore, a number of polyphenols, including quercetin, were shown to be mutagenic in cultured cells. A pro-carcinogenic effect of quercetin in rat models of nitrosomethylurea-induced pancreatic cancer or azoxymethane-induced colon cancer has been reported.<sup>85</sup> The majority of the studies carried out with quercetin in rodents, however, showed anti-carcinogenic effects.<sup>86</sup>

A final example concerns vitamin D.<sup>87</sup> The current adult RDA of 5  $\mu\text{g}$  (200 IU) per day seems within the context of genomic integrity inadequate. Daily intake of 1000 international units (IU) or 25  $\mu\text{g}$  of vitamin D<sub>3</sub> may well lower the risk of developing colon, breast, prostate, and ovarian cancers by up to 50 percent, as recently presented.<sup>88</sup>

In summary, the optimal amount of any type of micronutrients that is actually “mandatory” for the human organism is the amount that maximizes a healthy lifespan, which, in a number of cases, appears to be higher than the amount needed to prevent acute deficiency disease.<sup>89</sup> This contradicts the basic tenets of the regulatory research performed in Europe on the safety of micronutrients, and implicitly regards food supplementation as an unwarranted surplus to dietary requirements.

Some researchers, however, have unreservedly pointed out the long-term benefits of food supplementation with micronutrients in terms of low individual and societal costs and negligible risks.<sup>90</sup> In terms of excess exposure risks, a recent analysis in the Netherlands by the RIVM in Bilthoven suggests that, on average, there seems to be no need for concern about too high intakes of vitamins or minerals,<sup>91</sup> which, in any case, is dwarfed by drug toxicity.<sup>92</sup>

Micronutrient compounds cannot, in summary, be approached selectively from an excess toxicity standpoint as is done in the Food Supplements Directive. First, the regulatory perspective on health and safety expounded in Food the Supplements Directive—“a high level of protection for human life and health”—requires a toxicologically symmetrical approach of micronutrients. Second, the issue of genomic integrity and

the role micronutrients play therein strengthen this symmetrical methodology. Avoiding deficiency diseases, as is the focus of the RDA, seems a too minimalist approach of micronutrients, especially considering the stringent regulatory protective demands. Indeed, RDAs do *not* define an optimal level of *any* nutrient, as they are focused on deficiency–disease prevention. They are furthermore designed to meet the needs of healthy people and do *not* take into account special needs arising from infections, metabolic disorders, or chronic disease.

Third, the use of default UFs seems too cautious. It on the one hand draws on the toxicological linear dose-response model that, in all intents and purposes, is not suitable in the case of the micronutrients’ U-shaped dose-response curve.<sup>93</sup> Indeed, where the margins between necessity and toxicity are narrow, application of conventional UFs could result in recommended safe levels that would be below those that are essential. Conversely, default UFs currently used by risk assessors in relation to non-essential chemicals (synthetic chemicals like pesticides or more mundane products like phthalates in plastics<sup>94</sup>) are overly protective from the standpoint of the behaviour of the average chemical, and may in fact be too conservative.<sup>95</sup> Therefore, standard application of default UFs seems even more conservative in relation to SULs for micronutrients. Although we propose a symmetrical regulatory approach of micronutrient compounds, this does not imply that both sides of the equation carry equal weight, on the contrary. Fourth, therefore, as an overarching perspective on micronutrients, health risks are primarily related, historically, economically, and toxicologically, to deficiency. Therefore, in order to grasp the regulatory preferences as expounded in the Food Supplements Directive we need to discuss the position and role of the precautionary principle, which has center-stage within the complex of European food-legislation.

### **THE PRECAUTIONARY PRINCIPLE: AVOIDING RESPONSIBILITY**

Although we mention the precautionary principle as one of the main drivers of the Food Supplements Directive, the principle therein is not mentioned. However, with the installation of the European Food Safety Authority the principle was specifically referred to, and hence it takes prime position in the development of European regulation within the food area.<sup>96</sup> In order to come to an innovative policy proposal for food supplements one needs to tackle the issue of precaution. The main gist of precautionary thinking is best captured in the Rio definition that is considered the most authoritative among the many formulations of the precautionary principle that can be found nowadays:<sup>97</sup>

“... 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.”

The principle is presented as a way of handling modern risks, and is said to promote prevention, rather than cure. In essence the precautionary principle seeks to advance the timing and

tighten the stringency of *ex ante* regulation. On these sliding scale dimensions, regulation is “more precautionary” when it intercedes earlier and/or more rigorously to preclude uncertain future adverse consequences of particular human activities.<sup>98</sup> The axiom put forward by the precautionary principle is that implementation regarding risks to human health and/or the environment singularly results in the reduction or elimination of those risks.

A common characterization of the precautionary principle holds that it seeks to impose timely protective measures to prevent uncertain risks, i.e. risks as to which there is little or no data on their probability and magnitude. Uncertainty is a key element. Indeed, the precautionary perspective on knowledge is that scientific research needs to be focussed on guaranteeing safety, which has become a strategic requirement for new products and processes. As the European commission states in its communication on the precautionary principle:<sup>99</sup> “Countries that impose a prior approval (marketing authorisation) requirement on products that they deem dangerous *a priori* reverse the burden of proving injury, by treating them as dangerous unless and until businesses do the scientific work necessary to demonstrate that they are safe.” This approach of innovation is usually defended with the quote that “Absence of evidence of harm is no evidence of absence of harm,”<sup>100</sup> which, however, is a meaningless truism.<sup>101</sup>

The precautionary principle therefore typically shows strong scepticism with regard to the knowledge claims of science. This scepticism is very strongly developed in post-modern theories of science, where all knowledge is presented as “socially constructed”.<sup>102</sup> With the reversal of the burden of proof it can never be completely proven that for instance GMO food does *not* carry risks for humans and the environment. Examples for the impossibility of proving a negative can be generated at random and *ad infinitum*. This scepticism, however, is only one side of the precautionary culture. Reflecting a profound ambiguity, the other side of the precautionary attitude towards what science can and should offer is optimistic to the same extent that it is pessimistic. The goal of precaution is “to foresee and forestall”.<sup>103</sup> One can only believe that this objective is achievable if one has a strong belief in science’s ability to identify risks and offer means for their prevention.

The aspiration to prevent uncertain risks is, however, unachievable due to a problem common to virtually all formulations of the precautionary principle. From a logical point of view the Rio definition, as the most authoritative of definitions,<sup>104</sup> is meaningless, because the lack of scientific certainty, which is propounded to be unsolvable by the scientific method, deprives us of the possibility to calculate the costs and benefits of precautionary measures.<sup>105</sup> What’s more, the problem with the precautionary principle is that it does not provide any guidance whatsoever. As Sunstein explains:<sup>106</sup>

“The real problem with the Precautionary Principle . . . is that it is incoherent; it purports to give guidance, but it fails to do so, because it condemns the very steps that it requires. The regulation that the principle requires always give rise to risks

of its own-and hence the principle bans what it simultaneously mandates.”

Analyzed at this fundamental and logical level, the precautionary principle engenders an impossible arrangement: to decide on a “safe course” results in the formation of other and new risks, which, by definition, evokes a secondary precautionary response, *ad infinitum*. To break this infinite regress the application of precaution needs to be limited. Precaution therefore demands choice. One cannot be cautious on all fronts, as this would completely stifle any type of activity, including precautionary policy itself. By erratically selecting some target risk and focusing exclusively on that risk regulatory as well as scientifically (it has been argued elsewhere that the choices that are made in relation to the implementation of the precautionary principle is guided primarily by the so-called “cultural ecological critique” worldview<sup>107</sup>), regulators can construct a decision as to the proper course of action. Application of the precautionary principle “guided” by this approach involves choices of risks *en lieu* with the predominant worldview and results in policies that are blind for the negative external effects thereby created. As a result thereof precaution empowers bureaucracy: the regulatory exigency to intervene, although underpinned with scientific research, nevertheless, as a result of the diminution of scientific standards (the scepticism we pointed at above), is driven by other than scientific deliberations.<sup>108</sup>

This brings us back to the issue of food supplements. As is formulated in the Food Supplements Directive: “An adequate and varied diet could, under normal circumstances, provide all necessary nutrients for normal development and maintenance of a healthy life in quantities which meet those established and recommended by generally acceptable scientific data. . . .”

Therefore, in view of this statement in the Food Supplements Directive, food supplements are regarded as superfluous products that are, by default, only in need of excess toxicology regulation; a varied diet is more or less a guarantee for sufficient micronutrient consumption and thereby human health. The term “normal diet” begs the question of what exactly a normal diet is. The truism that we can obtain everything that we need from a balanced diet only holds if we in fact eat such a balanced diet consistently. The perspective here expounded by the EC therefore is tautological: adequate is by default adequate. How this adequacy can be achieved, and what that adequate diet would actually be like remains undiscussed. Moreover, factors impinging on the individual nutritional status are only partly related to the dietary intake on which the EC has its focus. Malabsorption (genetic or otherwise) and increased nutritional requirements (e.g. during a disease period) also greatly affect the nutritional status of individuals. However, these aspects are not considered.

Our contention is that within the precautionary context described above, the Food Supplements Directive is primarily focussed on secondary risk management. Regulators and (scientific) experts in the main are being made increasingly accountable for what they do and thereby are becoming increasingly preoccupied with managing their own risks. Particularly, secondary risks to reputation are becoming as significant as the

primary risks for which policies should in fact be devised.<sup>109</sup> The increasingly dominant regulatory culture of risk-aversion<sup>110</sup> therefore engenders a food supplements policy singularly focused on excess toxicity risks, while simultaneously lecturing the Europeans to “eat a normal healthy diet.” Therefore, the Directive avoids responsibility for the human health of European citizens: intoxication as a result of food supplements intake is an considerably more visible phenomenon, upsurged by the bias for negative information about possible health risks of products or activities,<sup>111</sup> compared to deficiency diseases that are not (and cannot be) related to any regulatory activities (European regulators are not responsible for the individual dietary habits of European citizens), yet have a far greater impact on public health.

As a final observation, in line with the above, the Food Supplements Directive institutionalises, as Burgess observed in relation to a number of examples in the UK and Europe, mistrust within the consumer culture.<sup>112</sup> Through the politicisation of the consumer in Europe, on account of the introduction of accountability as the market was deregulated in the 1980s with the obvious loss of governmental and political power, EU governments re-established their legitimacy. By means of this institutionalized mistrust, regulation of an in essence deregulated market can be established. The insistence on advance proof, with the aid of the precautionary principle, that products (in this case micronutrient food supplements) pose no risk to human health galvanizes consumer suspicion even further.<sup>113</sup>

### **OF COURT CASES, SCIENCE, AND THE PRE-EMPTING OF THE EUROPEAN MARKET**

Despite all the above-mentioned and other publicised critical comments on precaution, a recent court case ruling (joint cases C-154/04 and C-155/04) on the Food Supplements Directive explicitly refers to the precautionary principle as the discerning criterion.<sup>114</sup> As stated in the relevant paragraphs:

“67: The information provided by the claimants in the main actions in their written observations about certain vitamin or mineral substances not included on the positive list in Annex II to Directive 2002/46 is not such as to cast doubt on the merits of that explanation. It is apparent from it that at the time when the directive was adopted those substances had not yet been evaluated by the Scientific Committee on Food or that, at the very least, the committee continued to entertain serious doubts, in the absence of adequate and appropriate scientific data, regarding their safety and/or their bioavailability.

68: In those circumstances and in view of the need for the Community legislature to take account of the precautionary principle when it adopts, in the context of the policy on the internal market, measures intended to protect human health . . . , the authors of Directive 2002/46 could reasonably take the view that an appropriate way of reconciling the objective of the internal market, on the one hand, with that relating to the

protection of human health, on the other, was for entitlement to free movement to be reserved for food supplements containing substances about which, at the time when the directive was adopted, the competent European scientific authorities had available adequate and appropriate scientific data capable of providing them with the basis for a favourable opinion, whilst giving scope, in Article 4(5) of the directive, for obtaining a modification of the positive lists by reference to scientific and technological developments.

69: It is also necessary to state in that regard that, by virtue of Article 7 of Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (OJ 2002 L 31, p. 1), the Community legislature is entitled to adopt the provisional risk management measures necessary to ensure a high level of health protection and may do so whilst awaiting further scientific information for a more comprehensive risk assessment, as is stated in the 10<sup>th</sup> recital to Directive 2002/46.

70: Contrary to the contention of the claimants in Case C-154/04, a negative list system, which entails limiting the prohibition to only the substances included on that list, might not suffice to achieve the objective of protecting human health. Reliance in this instance on such a system would mean that, as long as a substance is not included on the list, it can be freely used in the manufacture of food supplements, even though, by reason of its novelty for example, it has not been subject to any scientific assessment apt to guarantee that it entails no risk to human health.’

This central quote of the ruling shows a number of things. First, precaution is only regarded within the context of the internal market and the protection of human health, where, of course, human health should prevail over economy. However, this view on micronutrients and the presumed risks involved *a priori* selects for scientific knowledge in league with the precautionary principle with its institutionalized mistrust and secondary risk management tendencies. More importantly, it ignores one of the basic tenets of European regulation, which in the case of micronutrients seems all the more ironic: “a high level of protection for human life and health.”

Second, the subsidiary and paradoxical role and functioning of science is highlighted in this quote. On the one hand, science should give definitive answers in relation to the issues of safety when a (new) micronutrient food supplement is brought to market. How this could be done when the precautionary principle is one of the basic principles is quite obscure. Conversely, how safe is safe enough, and what scientific results would be deemed sufficient? It can never be proven, and this cannot be emphasized enough, that micronutrient food supplements do *not* pose any risks to any consumers. As it is possible to prove that a particular risk exists, yet impossible to prove that any and all possible risks are absent, the precautionary principle is prone to

generate a *probatio diabolica*, which is impossible and thereby unlawful.

To make matters worse, the EC in its communication states that “measures adopted in application of a precautionary principle when the scientific data are inadequate, are provisional . . .” and that “the provisional nature is not bound up with a time limit but with the development of scientific knowledge.”<sup>115</sup> This in fact means, considering the fact, as said, that it is unachievable to prove that any and all possible risks are absent, that precautionary measures could well have a *permanent temporary* status.

Third and finally, the Food Supplements Directive, with its implicit recourse to precaution, pre-empts innovative economic parties. Scientific research done by an innovative market party can still be deemed insufficient by the European regulatory bodies, which therefore holds total rights to shape the market as it chooses. As precaution does not require credible scientific information to ban a certain product, economic parties are from a procedural and substance point of view left in the dark. This will obstruct a level-playing field, and will deprive economic parties from their rights to freely enter the European market.

The current perspective of the Food Supplements Directive on micronutrients simply won't do. The precautionary principle, apart from the fundamental critique expounded elsewhere by many,<sup>116</sup> has no place in the debate on micronutrients because of the U-shaped curve (presented in an inverted fashion in Fig. 2). Indeed, as we have shown, deficiency in terms of long-term health aspects (e. g. cancer and degenerative diseases) seems a much more interesting and worthwhile risk to consider when regulation is concerned. Ames is quite adamant when he states that:

“A metabolic tune-up through an improved supply of micronutrients is likely to have great health benefits, particularly for those with inadequate diets, such as many of the poor, young, obese and elderly. The issues discussed here highlight the need to educate the public about the crucial importance of nutrition and the potential health benefits of a simple and affordable daily multivitamin/mineral supplement. Tuning up metabolism to maximize human health and lifespan will require scientists, clinicians, and educators to abandon outdated models and explore more meaningful ways to prevent chronic disease and achieve optimum health. It is becoming clear that unbalanced diets will soon become the largest contributor to ill health, with smoking following close behind.”<sup>117</sup> Below we will develop a rational for a micronutrient policy that will merge the new developing micronutrient paradigm and in which with cost-benefit considerations are taken on board.

### TOWARDS A NEW POLICY

Keeney estimated in 1997 that approximately each \$5 million of regulatory cost induces a fatality if costs are borne equally among the public. If costs are borne proportional to income, ap-

proximately \$11.5 million in regulatory costs induces a fatality (in 1991 dollars).<sup>118</sup> Gerdtham and Johannesson estimated in 2002 that the income loss that will induce an expected fatality is estimated to be \$6.8 million when the costs are borne equally among all adults and \$8.4 million when the costs are borne proportionally to income (in 1996 dollars).<sup>119</sup> Cost-induced fatalities by definition disproportionately burden the lower social classes.

This is especially the case for micronutrients as dietary-habits of these social classes are known to be of a lower standard than on average would be required for a diet-healthy life-style.<sup>120</sup> The diet of the lower socioeconomic groups provides low-cost energy from foods such as meat products, fats, sugars, potatoes, and cereals yet has little intake of vegetables, fruit, and whole-wheat bread. The diet consumed by these socio-economic groups is lower in essential nutrients such as calcium, iron, magnesium, folate, and vitamin C than that of the higher socioeconomic groups.<sup>121</sup> Food selection is constrained by economic considerations, whereby healthy eating patterns will be necessarily compromised, which will result in nutritional inadequacy. For most micronutrients, amplification of the cost constraint resulted in a progressive decrease in nutrient density of the diet.<sup>122</sup>

In this context, stringent regulation of micronutrient food supplements has opportunity costs: striving to guarantee public safety in relation to excess toxicity, the foregone opportunity is the cost-effective reduction of micronutrient deficiencies and its concomitant short- and long-term health effects. Market failure, as the main focus of the Food Supplements Directive, seems therefore to be more than offset by government failure.

Applying both cost-benefit and cost-effectiveness analytic techniques, it is for instance estimated that folic acid fortification is associated with annual economic benefit of \$312 million to \$425 million. The cost savings (net reduction in direct costs) were estimated to be in the range of \$88 million to \$145 million per year.<sup>123</sup> Another example relates to vitamin D. The U. S. economic burden due to vitamin D insufficiency from inadequate exposure to solar UVB irradiance, diet, and food supplements was estimated in 2004 at \$40–56 billion, whereas the economic burden for excess UV irradiance was estimated at \$6–7 billion. These results suggest that increased vitamin D through UVB irradiance, fortification of food, and supplementation could reduce the health care burden in the United States, UK, and most likely elsewhere.<sup>124</sup>

As food supplements could be a relatively safe and cost-effective addition to the human diet,<sup>125</sup> how then should micronutrients best be regulated? When the “high level of protection for human life and health” is taken seriously, first, the breadth and depth (in other words integrity) of scientific knowledge in this field needs to be taken seriously. There should be no room for scepticism, nor should there be any room for scientism (the concept that science alone is capable of resolving genuine human problems, whereby all areas of human life can be reduced to science<sup>126</sup>). This is in line with a full-weight-of-evidence approach ideally expounded in risk assessment procedures, as a

result of which a precautionary bias towards excess toxicity is eliminated, as it is contradictory to the scientific method.<sup>127</sup> Second, therefore, a realistic regulatory approach of micronutrients cannot be founded on precautionary thinking as understood by the European Commission for reasons outlined above. Third, any rational regulatory approach has to decide on which level public intervention is justified, although within the “assessment paradigm” this is hardly ever explicitly addressed. This in effect addresses the tradeoff between market failure and government failure. It therefore may be prudent to recapitulate the words of John Stuart Mill:<sup>128</sup>

“Nevertheless, when there is not a certainty, but only a danger of mischief, no one but the person himself can judge of the sufficiency of the motive which may prompt him to incur the risk: in this case, therefore, (unless he is a child, or delirious, or in some state of excitement or absorption incompatible with the full use of the reflecting faculty,) he ought, I conceive, to be only warned of the danger; not forcibly prevented from exposing himself to it.”

The European society should be weary of the danger in setting up open-ended compulsorily regulatory structures (advanced by the precautionary principle). Few could resist expanding on the “exigencies of public health” if given official normative powers and unrestrained license to define. Obviously, the remarks made here contain value-judgements, which, however, need not be eschewed in view of the costs and benefits of food supplements regulation addressed above.

Keeping in mind the above, we propose the following tenets to compose a realistic policy for marketable food supplements:

- (i) cost–benefit context;
- (ii) *ex post* orientated;
- (iii) benefit orientated,
- (iv) innovation oriented, and
- (v) market oriented (level-playing field). The flow-chart presented in Figure 3 is descriptive for the policy-direction we envision:

Individuals make a choice to consume food supplements, rather than being unconsciously and involuntarily exposed to them as they are to food-endogenous compounds. Food supplements that come to market therefore need to be safe (e.g. in terms of carrying clear and simple indications for normal recommended intake). Even without the present regulatory context, this is a crucial exigency that food business operators and other economic parties must take seriously in view of issues of trust, liability, product safety and consumer protection. Conversely, when micronutrients are projected to be presented for medicinal use, then these products automatically fall outside the scope of our proposed policy format. As a matter of clarification, over-the-counter (OTC) medicines—medication that can be obtained without a doctor’s prescription, yet has been authorized through the proper regulatory channels—have traditionally been used to treat self-limiting minor ailments with medicinal compounds that therefore need only be taken for a limited amount of time

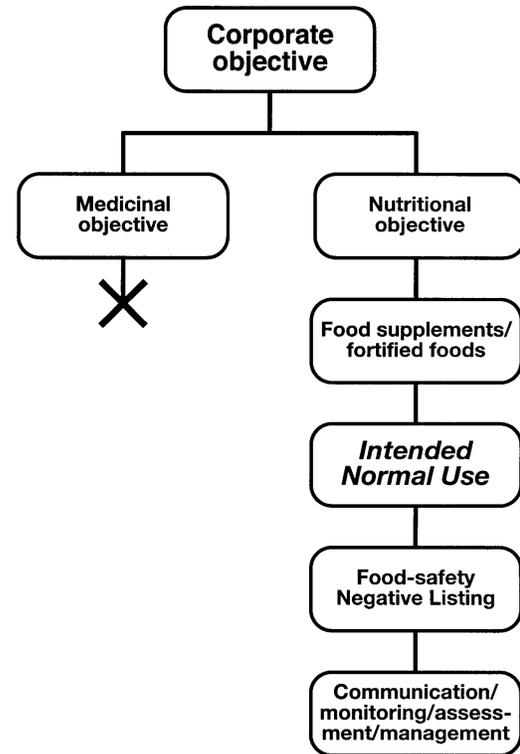


Figure 3 Flow-chart for food supplements regulation

and that are easy and relatively safe to us. The scope for treating such conditions has been extended by the rising switch from the prescription to the OTC status of effective treatments and this is likely to continue. The global trend is towards, and encouragement of, increased self-care including self-management of long-term conditions, which is counter to the approach taken by the Food Supplements Directive.<sup>130</sup>

The scheme presented in Figure 3 concerns micronutrients that are explicitly intended by the prospective producer to be used for supplementation of the diet and/or as additions to conventional foods. We stipulate that the term ‘micronutrient’ must be understood in the broadest possible way (see above). A priori, the scheme places all these micronutrients, including vitamins and minerals, in an *ex post* approach. In this approach, the essential ordering principle is the intended normal use (INU, the recommended daily dosage), as unambiguously clarified and presented by the manufacturer on the product’s packaging. This approach is borne out by the fact that, until now, the risk of overexposure to micronutrients has seemed limited.<sup>131</sup> In fact, taking into consideration the issue of household economics, people in general will not be capable of, or indeed willing, to invest in food supplements containing excessive quantities of micronutrients, as the costs would be prohibitive. Maximum levels are therefore superfluous in view of the fact that risks are minimal.

We therefore propose that through the system of INU of micronutrients, as established and presented by the relevant food business operator, food supplements should be allowed on the market without setting maximum and/or minimum levels.

RDAs, if applicable, should play a primary role in the presentation next to SULs with specific and serious safety concerns. The roles played by science and the history of safety, established as a result of long-term widespread use (tacit knowledge),<sup>132</sup> are different yet complementary and need to be internalized and explicated by the producer, whether through experimental scientific research, desk top studies, or both. We envision that the quality, purity (when applicable), consistency and stability of products will be guaranteed through GMP (good manufacturing practice) and/or other industry standards that match today's safety requirements and concerns. This is an important aspect of the safety-guarantee that producers need to assess, manage and communicate. What is more, compounds with a long-standing use, whether within or outside the EU,<sup>132</sup> could in principal be generally regarded as safe.<sup>133,134</sup> Tea, as an example, has been consumed literally for thousands of years, and it is this long safety record of tea consumption that makes the potentially beneficial compounds, present in tea, an attractive target for research and marketing.

In order to stimulate a level playing-field and innovative developments within the field of food, we propose this *ex post* approach to micronutrient compounds, whereby the aspect of safety is not tackled on the basis of politically dominated precautionary thinking, but rather on the basis of prevention, i.e. on the basis of verifiable scientific data concerning safety. Contrary to the precautionary approach, such an approach to safety would support and sustain innovative industry and thus, eventually, public health and the economies of the Member States and the Community at large. Positive listing through the no-data-no-market strategy will counteract innovation, as increasing regulatory demands, fuelled by precautionary deliberations, will hinder entry to the market, and continuing presence therein. This is illustrated in the EC communication on the precautionary principle, which states that the provisional nature of precautionary measures, which is usually a ban, "is not bound up with a time limit but with the development of scientific knowledge."<sup>135</sup> As mistrust in science is widespread,<sup>136</sup> scientific knowledge is hardly deemed sufficient to overcome the knowledge-barrier, so any precautionary ban will have an "enduring temporality." An effective way of counteracting this, therefore, would consist of a preventive negative list of compounds proved to be damaging to public health.<sup>137</sup> There are evidently good reasons to take a preventive regulatory approach with regard to safety, when confronted with products with only a very limited local or traditional use, and of which limited if any (scientific) knowledge is available. This reflects the overall approach that manufacturers need to be sure of the food safety of their product in relation to the recommended dosage (INU).

However, as is shown in our scheme, the primary responsibility, we believe, lies most (cost-) effectively with the producer and its objectives, the reason being that there is considerable evidence, as we have shown above, for health benefits of micronutrients at intake levels beyond the RDA, paralleled by the fact that few if any risks at intakes within or to some extent above dietary bounds have come or will come to the fore.<sup>138</sup> It

is likely that, in the future, the effects of nutrients on risk reduction of disease will be used increasingly to establish novel nutrient requirements.<sup>135,139</sup> In principle, recommendations for intake of nutrients to achieve such benefits could be based on a similar approach to that for establishing the RDA taken into account long-term benefits like for instance cancer and aging prevention. This then, in the light of the latest scientific knowledge, necessitates a new approach to the RDA, a n(ew)-RDA, in which the "survival" approach of the prevention of deficiency (as in the current RDAs) is transformed into a 'health' approach, that is the optimization of a healthy lifespan. In our view, a switch from the current deficiency-related RDA, limited to vitamins and minerals, to a health-related n-RDA, extended to other substances known to have beneficial effects on health, is essential in order to understand and address the optimization of the public's nutrient requirements. As stated by the Food and Nutrition Board in 1994: "The role of the RDAs at any time is to provide the best consensus of nutrition science interpreted into recommended values at that time. The FNB believes that the science of nutrition has advanced significantly, and the next edition of the RDAs will need to reflect this progress. One consideration is expanding the RDA concept to include reducing the risk of chronic disease."<sup>140</sup> To reiterate, current RDAs do not define an optimal level of any nutrient. The proposed switch will simultaneously address issues of safety, as n-RDAs will give guidance to consumers in terms of beneficial consumption levels, both with regard to supplements, fortified foods, and, ultimately, conventional foods.

Monitoring of public health in relation to the intake of micronutrient food supplements (analogous to the pharmacovigilance system for pharmaceuticals) is a further part of the proposed scheme. This is both of interest to governments as to producers, as it will reveal patterns of intake, associated risks and potential benefits.<sup>136,141</sup> Assessment and management options remain open to governments (but also producers) when monitoring studies reveal potential risks associated with intake of micronutrient food supplements.

In addition, communication is mentioned in the scheme. Independent scientific communication on health and safety issues surrounding micronutrients is, in our view, a viable strategy towards the general public that should not to be ignored. A key element in communication is the full-weight-of-evidence approach touched on above. It seems clear that public information concerning micronutrients, originated from an independent scientific body, could considerably optimize the public's knowledge of micronutrients concerning health and safety issues.<sup>137,142</sup> Disproportionate claims on health and consumption of certain food supplements can, within the context of proper communication, be scrutinised and publicly commented on with reference to the state-of-scientific-art.

The "locality" and values of science (the trans-scientific issues) are of importance here, even though these issues are not conveyed in the scheme. Although research papers by definition are an expression of scientific research as such, it is seldom realised that the locality and values of science

- (i) which research topics are selected,
- (ii) where research is done,
- (iii) who finances the research projects and
- (iv) to which end research is carried out—play a major part in the generation of scientific knowledge.

As Stenmark remarks: “. . . few scientists today seem to feel any need to be aware of the effects of various ideological [. . .] influences on the questions that are asked, on the gathering of data, and on the formulation and assessment of theories.”<sup>138,143</sup> This affects the scientific perspective on the issues here at hand: is scientific research risk or benefit, or both, regulatory, or just content driven, and are the scientific goals the marketing of “safe” and “beneficial” products, the governmental regulation of marketing, or other? The fact, for example, that limited knowledge is available on the toxicity of polyphenols is an expression of the perspective most researchers have here taken (namely health benefits). We are not questioning the validity of research results as such, on the contrary. However, we want to point at the focus of research efforts, which is influenced by other than scientific deliberations.

Weber asserts that results from scientific work is value-free if they do not contain, in the justification phase of science, any judgement of personal, cultural, moral or political value.<sup>140,144</sup> In this particular sense, science is worldview-neutral. However, values cannot, Weber emphasizes, be eliminated when it comes to what scientists choose to investigate, which hypotheses are to be preferred beforehand, or how scientific research results affect regulatory and public assertions. In this particular sense science is not worldview-neutral.<sup>140,145</sup> Within the field of micronutrients it should therefore be realized that the industrial, regulatory, but also the public health stakes are considerable, and that science in itself cannot be the judge in issues of safety, health and risks,<sup>141</sup> nor can it be used to emphasise a certain *a priori* perspective. As the United States National Research Council remarked:<sup>142,147</sup>

“Reliable technical and scientific input is essential to making sound decisions about risk. Scientific and technical experts bring indispensable substantive knowledge, methodological skills, experience, and judgement to the task of understanding risk.

. . . Good scientific analysis is neutral in the sense that it does not seek to support or refute the claims of any party in a dispute, and it is objective in a sense that any scientist who knows the rules of observation of the particular field of study can in principle obtain the same results.”

## CONCLUSIONS

As an opening remark we surmise that in relation to the benefits and risks of micronutrients, it seems clear that concerning the “assessment paradigm” implicitly expounded by the Food Supplements Directive, the significance of science, as a means to address issues of health and safety, has been inflated out

of proportion.<sup>143,148</sup> It wants to, among other things, address trans-scientific issues (value-judgements) through the scientific method, which is unachievable.

Policies directed at human health, should by definition be wary of the set goals, and the possibilities science and regulation have to offer. Usefulness of regulation is central here. The European Food Supplements Directive has at its fundamental goal the “high level of protection for human life and health”, which, however, is specifically translated in an asymmetric precautionary fashion; only excess toxicity is addressed. This then immediately shows the critical flaw, as risks are on all sides of the regulatory equation. For that reason, the precautionary principle, apart from our own reservations and critiques uttered by others elsewhere, has no place in the regulatory field of micronutrient food supplements. Focus on the risks of excess toxicity with recourse to the general acceptability of precaution generates the precautionary paradox: the caution that “should” give us pause causes harm, which we should pause before permitting to occur.<sup>144,149</sup>

From a risk management perspective the Food Supplements Directive, in our view, first and foremost caters for secondary risk management inclinations (liability and reputation) by explicitly referring to the “normal diet” as a sufficient source of the required micronutrients. In so doing, micronutrient food supplementation is implicitly regarded as superfluous. Therefore, the Directive openly avoids responsibility for the human health of European citizens: intoxication as a result of food supplements intake is an infinitely more “visible” phenomenon increased by the bias for negative information about possible health risks of products or activities, compared to deficiency diseases that are not (and cannot be) related to any regulatory activities, yet have a far greater impact on public health.

The model we propose limits governmental influences on the international market. This of course carries a value-judgement, which, however, is occasioned with costs and benefits deliberations. Governments need to set out the framework of health and safety, in which intended normal use and good manufacturing practice are fundamental. Market failure, as a primary occupation of precautionary culture, is not envisioned as a major problem when considering the micronutrients risks, which lie at the deficiency mark. In fact, when merely considering the issue of household economics, people in general will not be capable or willing to personally invest in food supplements in large quantities, as the costs would be prohibitive.

Micronutrient food supplementation need to be regulated in an *ex post* fashion, in which marketing objectives (supplementation of the diet) need to be clearly defined by the producer. Communication to the general public, if at all possible by an independent scientific body, could add considerably to the public’s understanding of micronutrients’ health and risk issues. Finally, it is our sincere opinion that in order to genuinely serve the public through regulation, the confines of regulation and the science which it requires need to be clearly spelled out by the scientists who are responsible for the elucidation of new fields of inquiry.

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- [20] Market failure, in economic theory, refers to the failure, in freely functioning markets, to deliver an efficient allocation of resources. The result is a loss of economic and social welfare. A number of reasons for market failure to arise are e. g. monopoly power (price is higher and output is lower under a monopoly than in a competitive market), and merit goods (goods and services that the government feels that people left to themselves will under-consume, and therefore needs to be subsidised at the point of use, examples being inoculations, public libraries, education and the like). In this particular case market failure is understood as the inadequate capability of a freely functioning market to generate a safe consumer environment for the production, marketing and consumption of food supplements.
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- [131] See e. g. note 91.
- [132] Tacit knowledge, opposite to codified (usually scientific) knowledge, is part and parcel of our daily lives and is transmitted through interpersonal contact, not through schoolbooks or scientific publications. Skills and traditions formed in laboratories, for instance, are utilized extensively, yet are not part of the codified output, such as journal publications and books. Therefore, even scientific knowledge in the public domain needs to be found, interpreted by specialists, and reprocessed for actual use. See Mokyr, J. 2002. *The Gifts of Athena. Historical Origins of the Knowledge Economy*. Princeton University Press, Princeton.
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- [140] Weber, M. 1949. *On the Methodology of the Social Sciences*. Free Press, New York. In the justification phase of science, scientists try to convince the rest of the scientific community of the adequacy of the explanations they have put forward through the different (scientific) platforms of communication in order to have their theories accepted as a part of the *corpus* of scientific knowledge. Here, worldview influences on science are the most problematical and counter–productive, as it distorts the process of science fundamentally. Theories should only be accepted by the scientific community in the light of considerations that involve transparent and reproducible empirical data, other (accepted) theories, and cognitive values such as consistency, simplicity, and explicatory power. Worldview (political and ideological) considerations, but also appeals to authority, consequences, force, and popularity –to name some of the argumentation fallacies– are illegitimate ways of deciding between theories. See note 29. See also: Polanyi, M. 1962. The republic of science: Its political and economic theory. *Minerva.*, **1**:54–73. Polanyi, M. 1963. The Potential Theory of Adsorption. Authority in Science has its Uses and its Dangers. *Science.*, **141**:1010–1013.
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