Micronutrients, Hormesis and the Aptitude for the Maturation of Regulation

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Abstract: The potential of hormesis as the default model to assess and manage chemicals is considered in relation to micronutrients. It is pointed out that micronutrients, despite their well-known U-shaped dose-response curve, are assessed and managed only with excess-exposure in mind. Hereby a schism between health and safety is unjustifiably realized. This proves to be the conundrum of basically all chemicals regulation. It is proposed that hormesis could in principle address this conundrum.

Key words: Hormesis, micronutrients, conundrum

INTRODUCTION

Risk is an influential aspect of modern-day society. Terrorism, food-safety, climate change, to mention just three disparate subjects, dominate media and politics. But before we get bogged down into undoubtely interesting sociological and philosophical deliberations, we will limit ourselves to chemicals and the risks involved therewith. We will critically reflect on the default approach of risks associated with exposure to chemical compounds with the aid of the physiological dose-response curve of micronutrients.

The age-old yet still prevailing Paracelcus axiom Sola dosis facit venemum-the dose makes the poison-does however not address the shape of the curve linking both ends of the exposure scale. Nevertheless, roughly two toxicological linear models dominate the scientific discourse. Model A depicts the no-dose no-illness approach when dealing with genotoxic carcinogens. The fact that chemicals are capable to react with hereditary material-thereby potentially inducing carcinogenesis-makes the assumption that even one molecule might in theory generate cancer seemingly viable. Model A is usually referred to as the LNT model (Linear Non-Threshold model)[1]. Model B assumes a threshold in the dose-response curve. So below the threshold the toxin is not assumed to generate any harmful effect in the exposed organism. Non-carcinogens are thought to usually exhibit such behaviour. Model B as a rule is referred to as the LT model (Linear Threshold model). Model C is referred to as hormesis and is not part of generic toxicological research Fig. 1. It nevertheless will be the topic of this research.

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
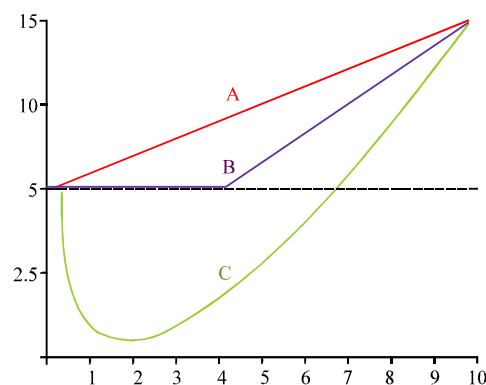

Fig. 1: Three toxicological models

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[2].

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 timeframe. Therefore, the overcompensation response may satisfy two functions: the assurance that the repair was adequately accomplished in a timely fashion and protection against subsequent greater insult. Possible mechanisms are multiple: enzymes that repair

damaged DNA, stimulated immune responses, apoptosis that eliminates damaged cells that would otherwise become cancerous and the like.

We need to define hormesis in a continuum of the dose-response curve. There are low-dose effects and high-dose effects of exposed organisms[3]. Low doses are stimulatory or inhibitory, in either case prompting living organisms to be dissociated from the homeostatic equilibrium that in turn leads to (over) compensation. For example, heavy metals such as mercury prompt synthesis of enzymes called metallothioneins that remove toxic metals from circulation and probably also protect cells against potentially DNA-damaging free radicals produced through normal metabolism[4].

High doses push the organism beyond the limits of kinetic (distribution, biotransformation, or excretion) or dynamic (adaptation, repair, or reversibility) recovery. This is the classical toxicological object of research usually required as a result of public and regulatory concerns whereby hormetic responses are by default regarded as irrelevant, or even contrary to policy interests and therefore unlooked for. Public concern about synthetic chemicals exposure seems to infuse public reluctance to view hormesis as a viable description of toxicological reality. Policymakers, similarly, are eager to address this concern and see no room for exploring the reality of hormesis and the possibilities of regulatory implementation: As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events[5].

Therefore, 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, subsequently modelled with linear assumptions. Risks of chemicals-exposure can thus be excluded from the public realm[6]. A primary reason to perform toxicological research as such in the risk-aware society can be summarised as follows[7]: '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 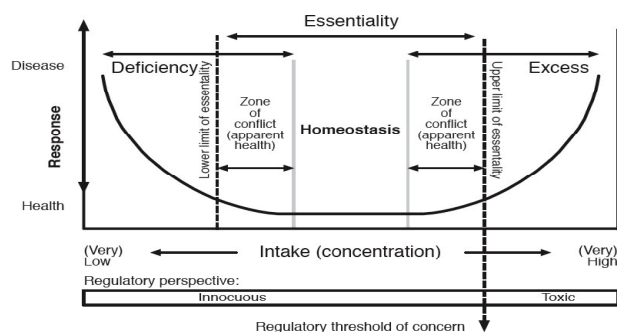to adequately protect public and environmental health by ensuring that risk is not likely to be underestimated. However, because there are many views on what adequate protection is, some may consider the risk assessment that supports a particular protection level to be too conservative (i.e., it overestimates risk), while others may feel it is not conservative enough (i.e., it underestimates risk). This issue regarding the appropriate degree of conservatism in EPAs 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.'

This is the default position essentially taken for granted and could be appropriately referred to as the toxicological risk paradigm. In the Kuhnian tradition this means that toxicological research as typified here is the standard research model with all its tacit knowledge and assumptions[8]. There is, however, a group of chemicals, with which we are accustomed to apply the U-shape curve instead of the linear dose-response curve within scientific enquiry: Micronutrients. These compounds will be our focus. We will try to elucidate the consequences of using a U-shaped curve and will try to see whether the physiological characteristics of micronutrients, such as vitamins and minerals, might be a route towards the maturation of regulation in such disparate fields as chemical and food safety, recommended daily allowances, environmental quality standards and the like. Therein, hormesis plays a central role. However, we will also show that despite the evident U-shape curve, European regulation on micronutrients in food supplements disregards the U-shape curve whereby as a result safety and health are unduly separated. This separation in risk regulation is the default approach we will criticise with the aid of the concept of hormesis.

Micronutrients: Science, markets and policy: (Micro) nutrient food compounds usually refer to vitamins and minerals, which are required by all living organisms in minute amounts, usually as part of an endogenous enzyme or a cell-produced catalytic protein. Commonly required minerals include for instance copper, zinc, molybdenum, manganese, selenium and iodine. Vitamins cannot be synthesized in the body in amounts sufficient to meet physiological needs and therefore must be obtained from the diet or from some synthetic sources. For this reason, vitamins and minerals are called essential nutrients. If a vitamin or mineral is present in the diet in insufficient amounts or is not properly absorbed by the body, a specific deficiency disease usually develops: scurvy in the case of vitamin C[9], rickets in the case of vitamin D[10].

There is a growing market for food supplements 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 products, e.g., teas. As the market for food (supplemental) products is expanding, in Europe the Food Supplements Directive (FSD, 2002) was implemented with its specific focus to approximate national European laws with a focus to safeguard human health of European citizens in view of the potential toxicity of excess intake of micronutrient food supplements[11]. Underlying this regulation is the toxicological perspective we discussed above and will rejoin below. This despite the fact that 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 as well as too high.
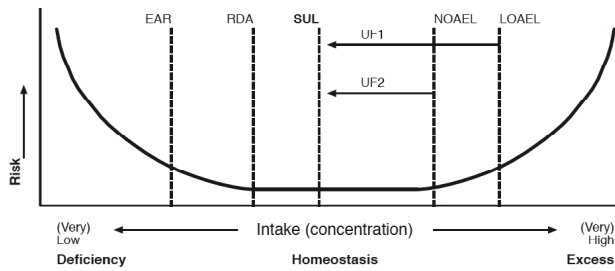
Below we have summarised the generalised physiological shape of the dose-response curve of essential micronutrients such as vitamins, minerals and other food borne bio-active compounds. The figure does not address deficiency and excess toxicology from a regulatory or experimental point of view but centres on the organism as it is exposed across a certain concentration range of micronutrients. For clarity, beneath the curve we have positioned the regulatory concerns within the European framework in relation to the physiological shape of the dose-response curve:

The curve represented here renders an idealised depiction of reality. The margin between essentiality and excess can range from a few-fold for trace elements such as selenium[12], to orders of magnitude for some of the B group vitamins such as biotin or pantothenic acid[13]. In practice, the magnitude and character of the adverse effects attributable to either deficiency or excess (toxicity) may differ, dependent on the shape and range of the curve.

Because of the essentiality of micronutrients, Recommended Dietary Allowances (RDAs) have been established for essential nutrients in order to prevent deficiency diseases, that is acute toxicity of deficiency. The pre-war twentieth century problems of poverty-induced undernourishment on account of economic depressions and looming war proved to be powerful drivers for the development of food standards, including the first standards for micro-nutrientsRDAs[14]. They denote the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97-98%) healthy individuals in a particular life stage and gender group. With this knowledge about the interaction between food and human health, research institutes and governments among others tried to address the primary risks of undernourishment-starvation, disease, infant mortality and the like. These risks to individuals and societies as a whole were real and pressing, in view of rising mortality and morbidity rates during economic depressions and the consequences of war[15]. The RDAs were designed to serve as dietary standards for the planning of food supplies for population groups. They are estimates of the daily average amounts of essential nutrients that individuals in a population group should consume over time in order to ensure that the physiological needs of all can be met[16].

In the history of food standards, the upper limits of exposure did not come into vogue until recently, as undernourishment as a result of poverty and war was dominant. Nowadays, with the growth of wealth and the increasing focus on healthy living[17], for the benefit of establishing policies for safe consumer products, so-called Safe Upper Limits (SULs) for the consumption of micronutrients are to be ascertained. SULs are predominantly defined as doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety[18]. Establishing SULs is usually carried out in the Deficiency-Excess model. At one end of the Deficiency-Excess model scale, where the levels of exposure decrease, i.e. at increasing levels of deficiency, the organism will suffer increasing harm. Here the RDA is the intervening standard that functions as an advisory criterion for the public. 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. Here the SUL functions as a regulatory standard for industry. Within the bandwidth of deficiency and toxicity-the D-E model is in actual fact a risk-risk model-a physiological optimum is assumed (homeostasis; see above). Below we depict a generalized model of micronutrient toxicology:

In order to establish Safe Upper Limits (SULs), standard toxicological approaches have been chosen despite the obvious U-shape of the dose-response curve. Historically, the no observed adverse effect level (NOAEL), that is the highest dose that in its adverse effects does not differ significantly from the control, has been used to establish human equivalent reference doses for potentially harmful effects of substances. The NOAEL (No-Observed Adverse Effect Level) and LOAEL (Lowest-Observed Adverse Effect Level) levels for micronutrient exposure are 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. In the application of UFs the derived UL should not be lower than the recommended intake. The obvious disadvantage of using NOAEL is that despite a range of doses tested, the NOAEL is by definition restricted to one of the chosen experimental dose levels[19].

Generally, values for uncertainty factors of 10 for intra-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 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).

Deliberations on risk within the field of micronutrients[20]: Micronutrients, despite their obvious physiological U-shape and concomitant 2-sided symmetrical benefits-risks profile, are scrutinised and regulated in Europe solely on their potential to harm the consumer as a result of excess intake: '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[21].' This means, is my contention, that the search for safety, on the one hand and the augmentation of human health on the other hand, although intimately related when considering micronutrients, are *a priori* and unduly separated in public policies and their underlying scientific assessments. This is quite clear when analysing regulation in the field of micronutrients[22]. Defining safe levels of consumption of micronutrients is at the centre of current regulatory efforts. Indeed, the European assessments of micronutrients excess toxicity-potential are an expression, as is stated in the FSD, of the high level of protection of consumers. Similarly, the communication from the commission on the precautionary principle describes a parallel goal of (precautionary) regulation namely the search for a high level of health and safety and environmental and consumer protection[23].

Contrary to the common understanding and European regulatory practice, micronutrients regulation requires a toxicologically symmetrical approach of micronutrients instead of a focus on excess toxicity. This is in fact underlined by the Healthy Life Years Structural Indicator (that is the number of years a person can expect to live in good health) as put forward in the Communication from the Commission Healthier Safer, more Confident Citizens: A Health and Consumer protection Strategy[24]. Without the symmetrical approach, this search for safety by the European regulators does for instance not include the diet of the lower socioeconomic groups. The dietary-habits of these societal classes are known to be of a lower nutritional standard than on average would be required for a diet intended to provide the basis for a healthy life[25]. Food selection is constrained by economic and socio-cultural considerations, whereby healthy eating patterns will be necessarily compromised, resulting in nutritional inadequacies and declining health[26]. For most micronutrients, amplification of the cost-constraint results in a progressive decrease in nutrient density of the diet[27].

This entails in my view that European micronutrients regulation includes other concerns than consumer safety and health. It needs to be reminded

that 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 [28], compared to deficiency diseases that are not (and cannot be) related to any regulatory activities other than advising the populace to eat healthy; a less than successful and naïve strategy[29]. The naivety and unsuccessfulness of such strategies has been recognised almost a decade ago by the DG Sanco (the Health and Consumer Protection Directorate) requested and subsequent ignored report on the future of scientific advice on food and public health. It is striking that in this advisory report nutrition, health and economic status are fully addressed[30]: 'To have scientific analysis on a European basis is important because currently many policy makers simply consider that the answer to tobacco problems is to educate the individual consumer not to start smoking. This naïve approach is evident in many other dimensions of public health, e.g. those relating to inappropriate diets in pregnancy; the substantial problems of low birth weight babies; the continuing challenge of iodine deficiency within the EU; the widespread anaemia in children and adult woman; the major issues relating to the health of Asians and other immigrant communities within the EU; the challenge of coping with escalating rates of adult chronic diseases and the huge and growing impact of the poor health of Europes elderly. In societal terms the health impact of societal deprivation, social exclusion and poverty is now becoming a major European issue which requires much more objective scientific analyses than are currently available. ...'

It seems clear that the current toxicological approach of micronutrients primary takes care of the increasing risk-aversion amongst the public[31] and the secondary risks of policies[32]. These other concerns than consumer health and safety seem central in European regulation. Indeed, when considering 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. This risk management of everything reflects the efforts of organisational agents formerly engaged in the collectivisation and pooling of social and economic risks of a primary nature, to separate from and re-individualise their own personal risk of a secondary nature. The result is a potentially catastrophic downward spiral in which expert judgement shrinks to an empty form of defendable compliance[33].

The artificial and *a priori* separation of safety and health in science and policy, as illustrated in the concise micronutrients example presented above is, I postulate, a prime issue to tackle in the field of toxicology and the standards derived there from. Below we will make some preliminary comments as how to bring safety and health together and what role hormesis could play therein. We will take the example of ethanol to illustrate our case

From risks to benefits-exemplifying the link between safety and health: With the micronutrients example we have illustrated the disjuncture between safety and health that exists in risk regulation. Despite the continuous nature of the physiological curve of micronutrients, this curve has been severed into two parts. Only the right part of the curve is deemed to require regulation, while simultaneously advising the European public to 'eat a healthy diet' [34]. This logic to regulate once toxicology elucidates a certain risk is occasioned by the implicit value-judgments we have addressed as public risk aversion and regulatory secondary risk management.

In my view the counterproductive disjuncture between safety and health can be amended by the implementation of hormesis as the default approach of risk regulation. In this final section we will illustrate this with the aid of ethanol regulation in the Netherlands. Clearly not a micronutrient in the traditional sense, the integration of health and safety could nevertheless attenuate the current regulatory approach of ethanol: 'Most human data on the effects of long-term exposure to ethanol concern the consumption of alcoholic beverages. Several epidemiological studies reported that the dose-effect curve for ethanol and overall mortality appears to be U-or J-shaped; beneficial effects due to the consumption of low levels of ethanol are observed, like a reduced risk of coronary heart disease. ... In this report, DECOS (Dutch Expert Committee on Occupational Standards) evaluates the effects of occupational exposure to ethanol. Although the committee acknowledges the fact that drinking alcoholic beverages might be a more important source of ethanol exposure, this exposure is not taken into consideration for the assessment of the effects after occupational exposure. ...[35]'

This quote from a report on ethanol from The Health Council of the Netherlands (Gezondheidsraad; an independent advisory body charged with providing Ministers and Parliament with scientific advice on public health matters), underlines the issue we have discussed previously on safety and health both in scientific risk assessments and subsequent policies. Not

known to be a human micronutrient, it nevertheless is quite known for its well-established U-shape in relation to e.g. cardiovascular disease and total mortality: 'The analysis reconfirms that the relation of alcohol drinking to total mortality is J-shaped, with reduced risk (mainly because of less cardiovascular disease) for lighter drinkers and increased risk for persons reporting more than 3 drinks per day[36].' It is also known for its high dose risks, such as liver cirrhosis and cancer.

Could we describe ethanol, then, as a micronutrient as it clearly has a U-shaped dose-response curve? No. It would confuse matters unnecessarily, yet underlines the problems involved in separating safety and health issues when assessing chemicals exposure. Why would it be that the Dutch Health Council does not consider the obvious beneficial effects of ethanol exposure when considering maximum exposure limits within the professional sphere when knowing full well that those limits are exceeded by moderate and healthy drinking behaviour? Indeed, why would European regulators concern themselves only with excess toxicity of micronutrients while deficiency is part of the scientific and regulatory equation considering the search for a high level of health and safety and environmental and consumer protection?

An obvious answer would be that the assignment given to the Council by the Dutch government did not involve taking stock of the beneficial aspects of ethanol exposure (either through beverage consumption or professional exposure). Additionally, in most risk analyses voluntary and involuntary exposures (activities) are separated, so involuntary exposure to ethanol should be viewed differently than voluntary exposure through drinking an alcoholic beverage. Starr has described this differentiation as follows[37]: 'In the case of voluntary activities, the individual uses his own value system to evaluate his experiences. Although his eventual trade-off may not be consciously or analytically determined, or based upon objective knowledge, it nevertheless is likely to represent, for that individual, a crude optimization appropriate to his value system. … Involuntary activities differ in that the criteria and options are determined not by the individuals affected but by a controlling body. Such control may be in the hands of a government agency, a political entity, a leadership group, an assembly of authorities or opinion-makers, or a combination of such bodies.'

This seemingly clear-cut differentiation is blurred when considering for instance drinking a cup of coffee. It is estimated that nearly a thousand chemicals are in a cup of coffee, of which fewer than thirty have been tested for cancer in rodents. Are coffee drinkers involuntary subject to the remaining hundreds of unknown chemicals with unknown toxicology? Or is human life full of unrecognized goods and bads? Hormesis, nowadays considered to be a well-established toxicological phenomenon, could in principle resolve the conundrum sketched here, provided that safety and health perspectives are *a priori* combined in the assessments of chemicals. Hormesis redefines our concept of pollution and contamination. It questions the premise that pollutants are unconditionally bad and therefore acknowledges that the human organism does have adaptive capabilities. This is innovative because modern environmental and public health legislation is built in large part on the moral dichotomies of good versus evil, clean versus dirty, natural versus unnatural, but also safety versus health. Chemical substances -be it natural or synthetic- are not either bad or good; they are both, depending on exposure levels and adaptive responses from the exposed organisms[38].

Therefore safety and health cannot be separated when evaluating the risks of chemicals. This is the lesson learnt from the micronutrients account given above (in a too concise a manner) and the example of ethanol in this final section. Policies on chemicals safety needs to shed the simplistic moral dichotomies of good and evil in order to be able to mature into regulation that truly addresses safety and health of citizens. Hormesis can evolve into the bridging toxicological concept[39], in which comprehensiveness of available scientific data incorporated in the proposed risk assessment is principal[40]. *A priori* exclusion of scientific knowledge and data is detrimental to the assessment process and endangers the public trust in science as a neutral endeavour that does not seek to support or refute any public or private stakeholder. The cases of micronutrients and ethanol are illustrative here. We can no longer indulge in an oversimplified message to the public that will not be believed[41].

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