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Chemical Sensitivity in the Elderly: Lessons Learned from Micronutrient Consumption in the Dutch Elderly Population

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Author's contribution

This work was carried out in collaboration between all authors. Author JVB headed the project. Authors HV, EHJ and EJMBR conducted the analysis and interpretation and author LGSH drafted the manuscript. All authors were involved in the early work and assisted with the interpretation of the results. Authors HV, EHJ and EJMBR were in charge of data management. All authors were involved in the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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ABSTRACT

A food consumption survey in the Dutch elderly population (51-69 years of age) showed an increased trend in micronutrient supplement intake (36.4%; 120/347 participants). Because data on chemical sensitivity in the elderly is lacking, evaluation as to whether the current uncertainty factor (UF) of 10 is sufficient to protect the elderly was investigated using the micronutrient consumption data in the elderly Dutch population as a case study. Theories of ageing, and differences in toxicokinetic and toxicodynamics are briefly discussed in the context of chemical sensitivity in the elderly. Evidence suggests that for the healthy elderly, no additional default UFs are recommended because the present UF of 10 is probably sufficient. However, more research is needed to ensure that there is no additional risk, particularly in the not-so healthy elderly population. Although there is a trend of increased consumption of micronutrient supplements (i.e. vitamins and minerals) by the Dutch population, the existing European legislation for micronutrients in fortified foods

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(Regulation 1925/2006) and food supplements (Directive 2002/46) is now being translated to simultaneously set maximum levels of micronutrients in foods and in supplements. For the healthy elderly, no foreseeable risk is expected due to the consumption of micronutrients. For the unhealthy elderly, the effects of micronutrient consumption are not yet known and therefore, dietary supplement intakes need to be continuously monitored with detailed questioning on health status, supplement and prescription drug use. In addition, the generation of an international and up-to-date database on the composition of available dietary supplements is needed to fill the current data gaps.

Keywords: Elderly; ageing; chemical toxicity; risk assessment; micronutrients.

1. INTRODUCTION

Traditionally, human risk assessment consists of selecting the no observed adverse effect level (NOAEL) or the benchmark dose (BMD) from a pivotal study with a critical effect and adding uncertainty factors (UFs) to account for inter-species kinetics (UF = 4), inter-species dynamics (UF = 2.5), variability in human kinetics (UF = 3.16) and variability in human dynamics (UF = 3.16); all combined to the traditional uncertainty factor of 100 used [1]. Given that in this modern and western society new chemical compounds and pharmaceuticals are constantly being developed, their potential hazardous effect(s) to the human population needs to be continuously investigated. Of particular importance is whether the intra-species UF derivation used to extrapolate from the average human to susceptible populations is sufficient to protect sensitive populations such as the elderly. In this review focus was given on the elderly population and their micronutrient consumption in The Netherlands.

Recent studies aimed at measuring human variability using a database of 60 therapeutic drugs to represent a variety of metabolic and elimination pathways to derive pathway-related UFs for each metabolic route and subgroup (i.e. neonates, elderly and healthy adults) suggests that in the elderly population, drug metabolism is significantly impaired, in comparison to healthy adults [2]. Another therapeutic drug pharmacokinetic database consisting of 46 drugs encompassing a variety of clearance pathways (phase I metabolism, phase II conjugation and renal excretion) and more than 4500 subjects for the evaluation of *in vivo* drug clearance, showed that individuals over the age of 60 had a greater drug half-life (up to 60% increase) and slower clearance (up to 50% reduction) [3]. This decrease in elimination of toxicants is possibly due to factors such as the reduction in liver mass, reduction in the activity of hepatic metabolizing enzymes, decreased liver blood flow and modifications in plasma drug binding; all associated with natural ageing process [4,5].

The elderly are heterogeneous with respect to the ageing processes and, in most instances, the deficit in the elderly relates more to the lifestyle and diseases than to the ageing processes itself. The inability to distinguish between intrinsic ageing, natural disease and toxic responses makes the question whether the elderly should be considered a sensitive group for risk assessment very challenging.

Even though there are clear indications that the elderly respond differently to chemical exposure compared to the average population due to physiological differences, the point to address for the Dutch government is whether a new policy should be set to protect the elderly. The aim of this paper is therefore to find a scientific basis for whether the elderly (> 55 years of age) should be considered a sensitive group and whether the traditional UF of 100 is sufficient to protect the elderly population against adverse effects.

In the Netherlands, the healthy life expectancy for men is 70 years of age and the healthy life expectancy for women is 73 years [6], in comparison to the life expectancy of 78 and 82 years of age, respectively. The period of 65 years of age up to 75 seems to be a critical period, given that surveys indicate that during this period men and women in the Netherlands have the highest reports that they don't feel well (e.g. don't feel healthy) [7]. In general, approximately 75, 70 and 65% of 45-64, 65-74 and 75^{+} year-old men, respectively felt healthy; and approximately 70, 62 and 50% of 45-64, 65-74 and 75^{+} year-old women, respectively felt healthy [7]. In 2005, in the Netherlands, the healthy life expectancy in men and women aged 65 has been estimated to be 10.4 and 10.9 years, respectively [8]. Therefore, in general when dealing with the healthy elderly population,

we are dealing with approximately 70-75% of 46-64 year-old individuals, with approximately 62-70% of 65-74 year-old individuals, and with approximately 50-65% of 75^{+} year-old individuals [7].

A recent food consumption survey in 2007/2008 of the Dutch elderly population (51-69 years of age) showed that micronutrient supplements were consumed on a regular basis by 36.4% (120/347) of the participants (25.8% of the men and 42.9% of the women). The supplements were composed of a single component (18%) or a multi-component supplement (42%). A market inventory in the Netherlands on 120 nutrient supplements for elderly revealed that the mean composition (P50) for vitE was 1.5-fold higher than the recommended daily allowance (RDA), the 95^{th} percentile intake (P95) value was up to 13.5-fold higher than the RDA and a maximum value was 26.8 times the RDA; although none exceeded the tolerable upper intake level of 300 mg/day but were still on the high end [9]. For vitC, the P95 value was found to be 4.38 times the RDA and the maximum value was 14 times the RDA [10]. These data illustrate that consumption of supplements by the elderly population may contribute to high nutrient densities. On the other hand, surveys dealing with micronutrient intakes in Europe indicate that the elderly are usually under-represented. Nevertheless, a survey from the UK of institutionalized and non-institutionalized individuals over 64 years of age, showed that in the majority of instances, the elderly intakes were below the lower reference nutrient intake (LRNI) [11]. Although the elderly-specific nutrient data is limited, the available data indicate that the elderly generally suffer from micronutrient deficiencies and that there is a trend of increased consumption of micronutrients, which, in some instances, may contribute to high nutrient densities, as in the case of vitE and vitC in the Netherlands. For this reason, the micronutrient consumption in the elderly Dutch population was taken as a case study to inform about chemical sensitivity in the elderly.

2. THEORIES OF AGEING

At present, in spite of intensive interest and significant progress in aging research, there is not yet a universal agreement on one specific theory of aging. On the contrary, the number of theories is large, some more favored by investigators than others, although in the final analysis, many if not all of these theories may work together. Here we highlight specific changes that may affect chemical sensitivity and possibly micronutrient uptake in the elderly.

Aging is a continuous and complex multi-factorial process that involves the interaction of genetic, epigenetic and environmental factors. It is widely accepted that physiological aging is the result of two opposing processes: (i) processes that destabilize the organism and increase the probability of diseases and death, and (ii) longevity assurance mechanisms that prevent, repair, or contain damage. Processes of the first group are often chemical and physico-chemical in nature or related to endogenous metabolic processes, and are either inevitable or only under marginal biological control. In contrast, protective mechanisms are partially genetically determined and are subject age-related changes [12,13].

An important genetic event that occurs during ageing is the accumulation of gene mutations resulting in differences in gene expression and possible alterations in the abundance and post-translational modifications of proteins [14]. Changes in the regulation of gene expression may also occur through modifications in the organization of DNA and protein with increasing age. Studies have shown increases in histone $H1^{0}$ with concomitant decreases in histone $H1^{I}$ and $H1^{II}$ in the heart, brain and liver in different species of mice as a function of age [15]. An assessment of histone acetylase activity in rats showed a 30 to 70% decrease in acetylation of histones with increasing age. This alteration of histone-DNA interaction makes DNA more prone to toxicant-induced damage. Further, [^{3}H]-acetate incorporation showed an age-dependent trend where histone H4 was pivotal in rats that were 2 months of age, while histone H3 is more pivotal in older rats (12, 16 and 24 months of age). Rats that were 27 months old showed equal levels of histone H3 and H4 [16]. Hence, there is an indication of age-dependent variation in chromatin maintenance and modulation that may affect the sensitivity to toxicants in the elderly.

Repair systems in the elderly may be significantly reduced, leading to an accelerated induction of mutations [17]. Studies have demonstrated that DNA mismatch repair (MMR) is significantly reduced in senescent cells through a significant down-regulation of human MutS homologue 2 (hMSH2) and MSH6 proteins; both important proteins that form heterodimers (MutSα-complex) and are involved in the initiation step in the MMR

pathway [18]. This senescence-dependent increase in genomic instability may account in part for the accumulation of genetic damage with increasing age. Other repair pathways have also been shown to be reduced with increasing age including base excision repair, nucleotide excision repair and double-strand break repair [19]. Repair enzyme levels responsible for the repair of alkylating mutagens such as 3-methyladenine-DNA *N*-glycosylase are significantly lower in older mice (15 to 17 months old), in comparison to young adult mice (7 to 8-week old) while the levels of O^6-methylguanine-DNA methyl transferase remain unaltered with increasing age [20]. The *in vitro* exposure of human peripheral lymphocytes from smokers to (±)-*anti*-benzo(*a*)pyrenediolepoxide resulted in an increase in lymphocytic DNA damage in older subjects presumably because of a decrease in lymphocytic excision repair capacity [21]. The increase in the frequency of mutations with age has been associated to a reduction of repair capacity towards reactive oxygen species-induced DNA damage [22], although recent studies have shown elevations in 8-oxoguanine DNA adducts from lymphocytes of individuals 63-70 years of age and 75-82 years of age, in comparison to individuals 20-35 years old [23]. In this study there was also an elevation in *in vitro* oxidative stress response with increasing age, as indicated by a pronounced decrease in the yield of breaks in lymphocyte DNA from anti-oxidant supplemented subjects treated with hydrogen peroxide [23]. Thus, repair enzymes activity changes with increasing age and may result in DNA hypersensitivity to toxicants.

The changes that occur during ageing are not limited to only changes in DNA alone but also in other macromolecules such as proteins and lipids. An increase in protein glycosylation resulting in a cascade of irreversible chemical reactions that lead to a decrease in the elasticity and permeability of extracellular compartments and impairment of the passage of nutrients and waste products out of the cell [24]. The glycosylation of DNA and RNA can also result in detrimental effects. Recent data indicate that toxicants, both environmental and generated endogenously by metabolism, are major contributors to macromolecular damage and physiological deregulation that contribute to aging. For instance, electrophilic carbonyl compounds derived from lipid peroxidation appear to be particularly important. As a consequence, detoxification mechanisms, including the removal of electrophiles by glutathione transferase-catalyzed conjugation, are major longevity assurance mechanisms [13]. In addition, elevated levels of oxidized proteins have been detected in tissues from patients with age-related diseases such as atherosclerosis, neurodegenerative disorders and cataracts, suggestive that their repair and complete catabolism to their amino acid components is inefficient [25]. Damaged proteins are degraded by the proteasome or through the collaboration of the proteasome with lysosomes. Incomplete degradation of heavily modified substrates may accumulate within the lysosomal compartment to form lipofuscin-like aggregates and the accumulation of these aggregates results in impaired turnover of proteasomes and mitochondria, destabilization of lysosomes, leakage of proteases into the cytosol and apoptosis [25].

Overall, age-dependent variation in chromatin maintenance and modulation, repair enzymes activity deficiencies and incomplete degradation of heavily modified substrates may result in hypersensitivity to toxicants in the elderly and may possibly also affect micronutrient uptake.

3. FACTORS WHICH MAY AFFECT CHEMICAL SENSITIVITY AND POSSIBLY MICRONUTRIENT UPTAKE

Although there are many physiological processes that are altered during ageing, focus will remain on age-related toxicokinetic changes that may have a significant impact in xenobiotic metabolism including absorption, distribution, metabolism and excretion in the elderly. In general, only some phase I enzymes e.g. esterases and some cytochrome P450s (CYP2C19) appear to be impaired in the elderly, while phase II reactions are not extensively affected, with the exception of a reduction in the glucuronidation capacity seen in the frailty-associated population.

3.1 Absorption

Absorption of chemicals and uptake into the blood occurs primarily via skin, lung and the gastrointestinal (GI) tract. Alterations in structure and function of these three organs clearly occur with age [12,26]. Several studies have indicated a decline in human skin permeability in elderly. The percutaneous absorption of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and 2,3,4,7,8-pentachlorodibenzofuran has been shown to be significantly decreased in older animals [27].

Little is known about effects of ageing on lung absorption, however, a decrease in the rate of alveolar-capillary gas exchange in elderly has been reported with greater body weight and lung volume changes [28]. A reduction in gastric acid secretion is commonly seen in the elderly [28]. The increase in pH alters the ionisation of compounds, enhancing or reducing their ability to diffuse passively across cellular membranes [28]. Decrease in gastric motility can prolong the transit time of chemicals in the gut thus enhancing their potential for absorption. However, GI absorption of xenobiotics is predominantly by passive diffusion and age-related changes in oral absorption of xenobiotics are not commonly seen. Active transport of molecules such as glucose appears to decrease with age, presumably as a result of a reduction in the number of sodium-linked glucose carriers [29,30]. The active transport of other small molecules such as calcium, phosphorus, galactose and iron has also been reported to decrease with age [12]. Overall, the limited available data suggests that subtle changes occur in absorption in the elderly.

3.2 Distribution

The distribution of chemicals throughout the body is governed by physiological changes that occur during ageing and the physico-chemical properties of the xenobiotic. The loss of body water and lean body mass with age results in a decrease in the volume of distribution for water-soluble compounds leading to enhanced toxicity, e.g. for ethanol [31] or ethylenediamine [32]. The higher percentage of body fat results in an increased accumulation of fat-soluble toxicants [33]. Lipophilic molecules rapidly pass across cellular membranes and accumulate in lipid rich tissues. Since adipose tissue volume increases but blood flow decreases with age, lipophilic compounds tend to show greater retention in the elderly (e.g. for polychlorinated biphenyls and halogenated solvents) [33]. Therefore, fat-soluble toxicants will have increased volume distribution and require a longer period of time in reaching steady state and be eliminated. Decreased cardiac output with age may also result in slower delivery of toxicants to the liver and kidney [33].

3.3 Metabolism and Excretion

There are several physiological changes that occur during ageing which can influence biotransformation reactions both in the liver and in extra-hepatic tissues (e.g. portals of entry, skin, respiratory tract, GI tract). However, few clear patterns exist concerning age-related changes in biotransformation because metabolic changes with ageing tend to be substrate, sex, strain, and species-dependent [12,26,34]. The decreased liver mass and up to 50% reduction in hepatic blood flow may result in a reduction in drug clearance while the reduction in albumin levels may alter the proportion of plasma protein binding and the volume of distribution of some xenobiotics [26,34].

Several age-related changes in cytochrome P450 levels have been shown particularly with CYP2C19, CYP2D6, and CYP3A4 [2]. The half-life of drugs metabolized by hepatic cytochrome P450s or through renal elimination has been shown to be between 50-75% longer in older than younger adults. Longer half-lives are also detected in liver or kidney disease [3]. For this reason, the elderly are at increased risk of drug interactions and side effects [35].

Generally, there is an age-related reduction in phase I reactions (e.g., oxidation, hydrolysis, reduction) and first-pass hepatic metabolism, while phase II reactions (e.g. glucuronidation, sulfation) are not usually affected by ageing [36]. The concentration of glutathione levels in the liver and kidney of aged rats (20 months of age) has been shown to be significantly lower (liver: 1.65-fold and kidney: 2.29-fold) than in young rats [37]. In addition, elderly rats had more DNA damage (liver: 1.84-fold and kidney: 1.86-fold increase in DNA migration in the comet assay) in comparison to young (9 weeks of age) rats [37]. These changes in the activity and/or concentration of drug metabolizing enzymes are important factors that account for differences in drug/metabolite exposure in the elderly population [38].

The livers of the elderly show a general decline in adaptive responsiveness and reduced reserve capacity, although clinical tests indicate that, in general, liver function is well maintained in this age group. Nevertheless, the changes in metabolic capacity may affect the kinetics of a chemical. For instance, the bioavailability, plasma concentration and half-life of a chemical may increase due to age-related changes in liver function and this may have consequences for the toxicodynamic effects of a chemical on target organs.

Finally, excretion of toxicants generally occurs in the kidney. Glomerular filtration decreases in the

elderly as a result of decreased renal blood flow, loss of nephrons and decreased kidney size, and may result in prolonged exposure in the blood of xenobiotics that are eliminated by renal excretion [33].

Even though there are clear indications that the elderly may respond differently to chemical exposure compared to the average population because of toxicokinetic (drug/chemical disposition) and toxicodynamic (sensitivity) differences, no additional default UFs are recommended because the present UF is probably sufficient to protect the healthy elderly. It is recognised that in order to always cover the most sensitive person exposed to any chemical would require a very large default UF. That is of course not workable and it is usually assumed that a default UF of 10 is sufficient to protect the larger part of the population, including e.g. the elderly. For threshold effects, this factor of 10 is the standard procedure, as a default, when assessing exposure to the general population [39]. Additional UFs should nevertheless be applied on a case-by-case basis if the toxicological database indicates that the default UF of 10 for intra-species variability is insufficient to adequately safeguard the elderly population (or any other subpopulation). However, more research is needed to ensure that there is no additional risk, particularly in the not-so healthy elderly population. The effects of chronic exposure to high doses of toxicants in the elderly population also need to be investigated, especially if these are lipophilic or require inactivation by renal excretion.

4. DUTCH POLICY ON MICRONUTRIENT CONSUMPTION

Because data on chemical sensitivity in the elderly is lacking, evaluation as to whether the current uncertainty factor (UF) of 10 is sufficient to protect the elderly was investigated using the micronutrient consumption data in the elderly Dutch population. The Dutch policy was surveyed in order to investigate whether the increased trend of supplement intake in the elderly might lead to over-consumption. Dutch policy for micronutrient intake is geared towards preventing deficiency and over-consumption through the establishment of dietary reference values. These dietary reference values comprise of 1) an estimated average requirement (EAR) no data specific for elderly [43]. Dutch policy for micronutrient intake is geared towards preventing deficiency and over-consumption [41]. Existing which is the adequate requirement for 50% of the population; 2) a recommended daily allowance (RDA) which is the average daily intake level to meet nutritional requirements of 97.5% of healthy individuals (equivalent to the mean or EAR plus 2 SD); 3) a tolerable upper intake level (UL) which is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans; and 4) a LRNI which is the amount of a nutrient which is adequate for only 2.5% of the population group and represents those with the lowest need (Fig. 1).

Although for micronutrients the risk of adverse effects is associated with consuming too little (deficiency) or too much (over-consumption), this report will focus only on the latter. Dietary reference standards for evaluating and managing the risk of excessive intakes of vitamins and minerals have been established recently for a number of vitamins and minerals and are referred to as UL (sometimes also called Safe Upper Levels). The UL is the maximum level of total chronic daily intake of a nutrient from all sources including foods, water, nutrient supplements and medicines judged to be unlikely to pose a risk of adverse health effects to almost all individuals in the general population [41]. The term 'tolerable' implies a level of intake that can be physiologically tolerated by humans. ULs may be derived for populations in different life stages, for instance infants, children, adults, pregnant and lactating women by using relevant data or, in the absence of data for a particular life stage group, by extrapolating from the UL for other groups, e.g. for children on the basis of body weight. ULs have been derived for a number of vitamins and minerals, the most relevant now is from the EFSA [42]. The UL is not a recommended level of intake but rather is an estimate of the highest level of intake that carries no appreciable risk of adverse health effects. The UL is not meant to apply to individuals receiving the nutrient under medical supervision or to individuals with predisposing conditions which render them especially sensitive to one or more adverse effect(s) of the nutrient, e.g. those with genetic predisposition or certain metabolic disorders or disease states.

There is a trend of increased consumption of micronutrient supplements (i.e. vitamins and minerals) by the Dutch population, but there are European legislation for micronutrients in fortified foods (Regulation 1925/2006) and food supplements (Directive 2002/46) is now being

translated into simultaneously setting maximum levels of micronutrients in foods and in supplements [44]. This setting of maximum levels in fortified foods and in food supplements involves the assessment of the margin between the amount of a micronutrient present from basic food intake (e.g. at 95-percentile) and the UL. The maximum amount of a micronutrient that may be added to fortified food and/or food supplements with little risk of adverse health effects in the population is therefore the UL minus the 95-percentile. Prior to setting maximum levels for fortified foods and food supplements a risk management decision needs to be taken whether to allow this maximum amount for fortified foods only, for food supplements only or for both (e.g. in a 50/50 ratio) (Fig. 2).

There are well-developed methods for setting maximum safe levels of food fortification, the latest therefore being developed by RIVM [45]. There is also methodology for setting maximum safe levels in food supplements [46], but this has thus far not really been scientifically challenged [11]. Maximum levels in fortified foods and food supplements can and need to be set for age- and gender-specific groups.

In the Netherlands, the healthy elderly population comprises of approximately 70-75% of 46-64 year-old individuals, 62-70% of 65-74 year-old individuals, and 50-65% of 75^{+} year-old individuals [7]. For these individuals, no foreseeable risk is expected due to the consumption of micronutrients from supplements, dietary intake and other sources.

On the other hand, the not-so healthy elderly comprise of approximately 25-30% of 46-64 year-old individuals, 30-38% of 65-74 year-old individuals, and 35-50% of 75^{+} year-old individuals [7]. These individuals may be taking daily prescription drugs to combat chronic diseases such as diabetes, circulatory or respiratory diseases. The effects of micronutrient consumption from supplements, dietary intake and other sources for the unhealthy elderly are not yet known. For this reason, dietary supplement intakes need to be continuously monitored using a combination of dietary recall methods with detailed questioning on health status, supplement and prescription drug use in the elderly population. In addition, the generation of an international and up-to-date database on the composition of available dietary supplements is needed to fill the current data gaps.

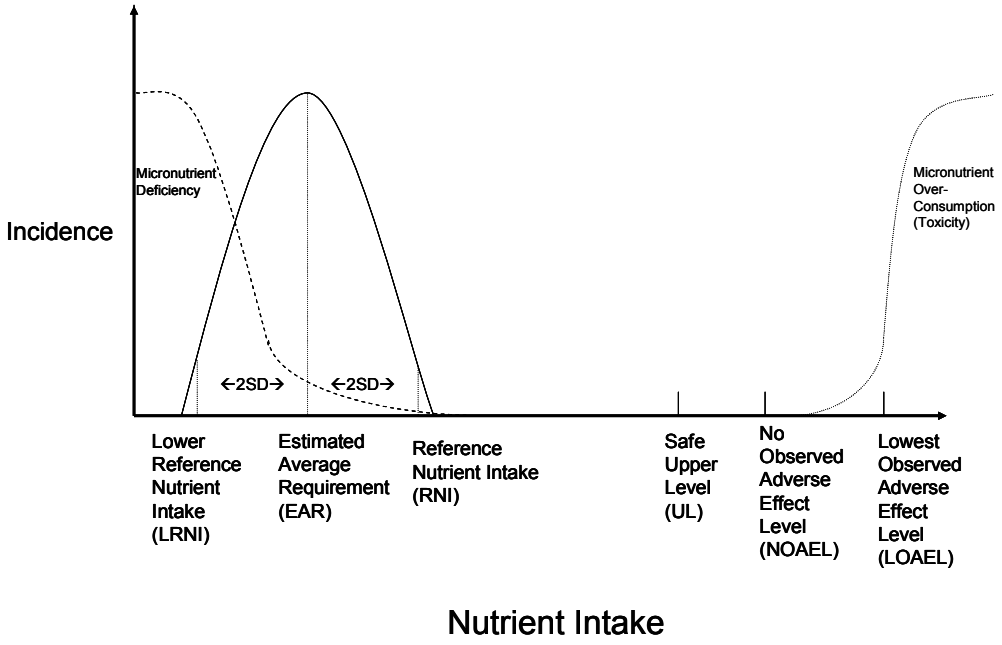

Fig. 1. Model for assessing dietary reference values for micronutrients
(Adapted from [40]; SD = Standard deviation)

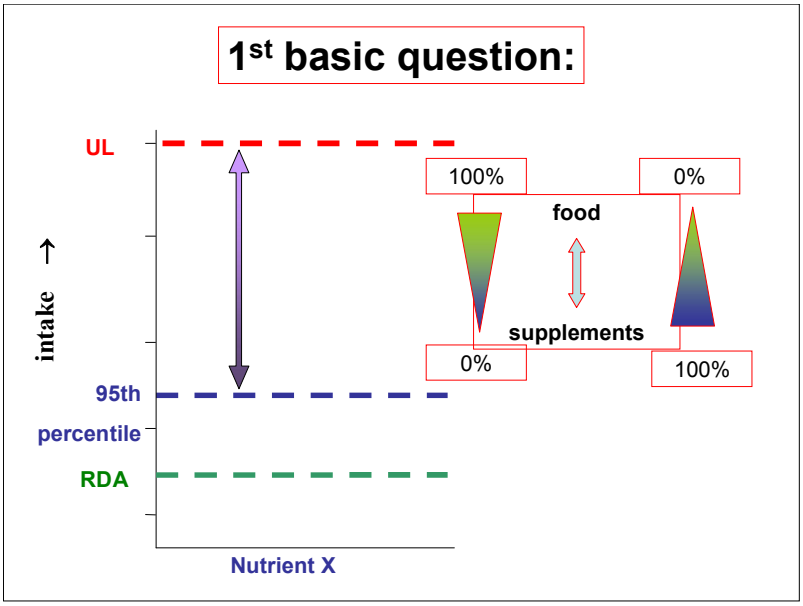

Fig. 2. Depiction of risk management scheme for the setting of maximum levels in fortified foods and food supplements

5. POTENTIALLY SENSITIVE SUB-POPULATIONS

Although this paper deals with the 'healthy elderly' populations, it is important to be aware of the existence of potential sensitive sub-populations among the elderly. The major causes of death in the Netherlands include cancer (41%), circulatory diseases (41%), respiratory diseases (14%), psychological disorders (6.4%), digestive disorders (5.4%), external causes of injury and poisonings (5.3%), and endocrine disorders as a result of dietary, metabolic diseases or immune disturbances (4.1%) [7]; all of which may be in one way or another exacerbated by chemical toxicity in the elderly. Of particular importance is diabetes because the prevalence increases exponentially after the age 40, with type II diabetes being the most common [47]. The prevalence of type II diabetes increases from 68 cases per 1000 per year in 45-64 year-old males to 171 cases per 1000 individuals per year in 65-74 year-old and in 75^{+} year-old males [47]. Similarly, the prevalence of type II diabetes increases from 48 cases per 1000 per year in 45-64 year-old females to 140 cases per 1000 individuals per year in 65-74 year-old females, and 165 cases per 1000 individuals per year in 75^{+} year-old females [47]. Immigrants with Surinam, Indonesian, Turkish or Moroccan origin are at greater risk of developing type II diabetes than the native Dutch population [48]. An early indication of diabetes is the metabolic syndrome where lipid status is a major influential component. There is a remarkable age-related difference in the serum concentration of some lipid parameters (triglycerides, free fatty acids) between men and women. At 20 years of age women have a relative healthy pattern (low concentration of lipids) but their lipid levels increase dramatically with age to levels comparable to those seen in men [49]. This rapid increase in lipid parameters may make women more prone to diabetes as they get older. Among other consequences, diabetes is known to impair renal function, and as a result may have a direct impact on chemical sensitivity. Therefore individuals with the above mentioned disorders, immigrants or sex may be potential sub-populations that need to be considered or at least kept in mind.

6. CONCLUSION

Although there is a trend of increased consumption of micronutrient supplements (i.e. vitamins and minerals) by the Dutch population, there are currently no elderly-specific data available. In the Netherlands, the healthy elderly population comprises of approximately 70-75% of 46-64 year-old individuals, 62-70% of 65-74 year-old individuals, and 50-65% of 75^{+} year-old individuals. For these individuals, no foreseeable risk is expected due to the consumption of

micronutrients from supplements, dietary intake and other sources when existing European legislation for micronutrients in fortified foods (Regulation 1925/2006) and food supplements (Directive 2002/46) is simultaneously translated into setting maximum levels of micronutrients in foods and food supplements.

On the other hand, the effects of micronutrient consumption from supplements, dietary intake and other sources for the unhealthy elderly are not yet known. For this reason, dietary supplement intakes need to be continuously monitored using a combination of dietary recall methods with detailed questioning on health status, supplement and prescription drug use in the elderly population. In addition, the generation of an international and up-to-date database on the composition of available dietary supplements is needed to fill the current data gaps.

With regards to chemical sensitivity in the healthy elderly, even though there are clear indications that the elderly may respond differently to chemical exposure compared to the average population because of physiological differences, no additional default UFs are recommended because the present UF is probably sufficient to protect the healthy elderly. Additional UFs should nevertheless be applied on a case-by-case basis if the toxicological database indicates that the default UF of 10 for intra-species variability is insufficient to adequately safeguard the elderly population (or any other subpopulation). However, more research is needed to ensure that there is no additional risk, particularly in the not-so healthy elderly population. The effects of chronic exposure to high doses of toxicants in the elderly population also need to be investigated, especially if these are lipophilic or require inactivation by renal excretion.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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