alliance for natural health

"Good Science, Good Law"

ANH INNOVATORS CLUB BULLETIN

Aug/Sept 2006

Regulatory Developments

European Union

European Commission consultation re Maximum Permitted Levels

The issue of "scientific risk assessment" in the context of nutrients is one of the single most important issues affecting the fate of natural healthcare today. The issues that we discuss below relating particularly to developments, both in Europe and in Codex, have massive implications on the way in which Regulators will control the use of natural products worldwide. Therefore this is just as relevant for companies within Europe as it is for companies in the USA, Australasia and other parts of the world.

Risk assessment of nutrients is presently under scrutiny as the means of determining both Upper Safe Levels and the even more important regulatory end-point, Maximum Permitted Levels, in Europe.

However, it will also be used as the basis for permitting, or banning, particular ingredients (e.g. nutrients, phytochemicals) in natural products used in healthcare.

The ANH was the first organisation associated with the natural products industry to identify that the scientific methods used in risk assessment and employed by organisations such as the US Institute of Medicine and the EU's Scientific Committee on Food (now absorbed within the European Food Safety Authority) were flawed. This position was made, with extensive support from the peer reviewed evidence base, in the ANH's consultation response to the FAO/WHO nutrient risk assessment project in December 2004.

Since this time, a Netherlands-based risk assessment institute, the HAN Foundation, under the sponsorship of ANH Innovators Club member, the International Nutrition Company, has taken up the issue and confirmed the irrational and unscientific nature of risk assessment systems and already one paper has been published (in *Environmental Liability*), while a further two papers have been accepted (one in *Environmental Liability*, the other in *Critical Reviews*). Further papers are in preparation.

The ANH is one of several industry stakeholders in Europe to be making a submission, due 30 September, to the European Commission in relation to its consultation on the setting of Maximum Permitted Levels. We have also attended and been very active in stakeholder consultations with the UK competent authority, the Food Standards Agency.

Given the importance of this issue, and the many misunderstandings both among consumers, practitioners and even in some sectors of the industry, we are devoting a significant section of the present Bulletin to this issue.

Alliance for Natural Health
The Atrium, Curtis Road, Dorking, Surrey RH4 1XA, United Kingdom
e-mail: info@anhcampaign.org tel: +44 (0)1252 371275
www.anhcampaign.org

Reg. Office: Unit 5, Forge End, St Albans, Hertfordshire AL2 3EQ, United Kingdom. A Company Limited by Guarantee Reg No. 4438769

Which organisations are responsible for risk assessment methodologies?

There are four main organisations that are exerting overriding control of the agenda on risk assessment internationally:

1. **FAO/WHO** – their expert panel produced a key report on methodologies for setting "upper intake levels" in January 2006 (http://www.who.int/ipcs/highlights/full_report.pdf). ANH provided one of 16 consultation responses reviewed by this expert panel (see www.alliance-natural-health.org/_docs/ANHwebsiteDoc_121.pdf).

2. **Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU)**. Dr Verkerk acts as the Scientific Advisor on the US National Health Federation's delegate panel. This is the only health freedom organisation with delegate status at Codex (since the NHF was admitted, all other applications, including that of the ANH, have been rejected!) The next meeting is in November in Thailand (assuming recent troubles don't lead to a postponement). Since Codex operates on a one country member / one vote principle, the single most influential player in Codex is the European Commission which has been given responsibility of voting on behalf of all 25 EU Member States. Therefore, one European Commission vote cast against a USA vote, represents a 25 against 1 vote!

3. **European Food Safety Authority.** This is the lead scientific/regulatory body establishing methodologies affecting food safety in Europe. On 13/14 July EFSA held a colloquium on risk/benefit assessment with 80 scientists participating, including Dr Verkerk. All of ANH's key areas of criticism of existing models were taken on by the relevant Discussion Group and proceedings of the colloquium will be published in March 2007.

4. **Food & Nutrition Board/Institute of Medicine.** The FNB established a model in 1998 which has been used to produce Tolerable Upper Intake Levels (ULs) and subsequently Dietary Reference Intakes (DRIs) for use in the USA. Nevertheless, the FNB/IoM are looking closely at developments in Europe and Codex and are directly involved in providing inputs. There is increasing interest in harmonising risk assessment methods internationally, and it seems likely that those methods accepted by Codex will become the predominant risk assessment methodology worldwide, including in the USA .

BfR-influence is disproportionate

Given the significance of both Codex (through the CCNFSDU) and the EU (through the European Commission and EFSA) in the development of risk assessment procedures, it is of great significance that the CCNFSDU is headed by Prof Rolf Grossklaus of the Federal Risk Assessment Institute (BfR: Bundesinstitut für Risikobewertung) in Germany, while the European Commission and EFSA are highly dependent on the views of another BfR scientist, Prof Hildegard Przyrembel.

None of this would be problematic if the methods that were being pushed by the BfR were scientifically rational. However, there is increasing scientific consensus outside the very closed world of European risk assessment in relation to foodstuffs, that key aspects of the BfR methodologies are flawed.

What's wrong with the proposed EU risk assessment model?

- The model has two main parts (se Figure 1 below), the first determines the Safe Upper Level (SUL), the second the Maximum Permitted Level (MPL), the latter being most important from a regulatory point of view as it will set the maximum daily dose available for sale

- The SUL is derived by taking a level that is known from scientific studies to be safe (the No Observable Adverse Effect Level) and dividing this by an arbitrary Uncertainty Factor, which might be 3, 10 or even 100. The process by which the USL is derived has been endorsed by the Expert Panel of the FAO/WHO[1]

[1] Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment WHO Headquarters, Geneva, Switzerland, 2-6 May 2005, *A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances*, FAO/WHO, 11 January 2006 (http://www.who.int/ipcs/highlights/full_report.pdf).

- The MPL starts with the USL but then reduces it further by subtracting the amounts found in typical diets, which may include fortified foods. Further allowances are made for sensitive population sub-groups, based on studies which may not be applicable to the bulk of the population

- Existing models 'pool' nutrients in groups so that the maximum level of the most toxic form of nutrient is then applied to all other forms in the same group

- In this way, intakes of a more toxic form of a vitamin or mineral will limit the level of less toxic forms e.g. the level set for iron sulphate will be used for the less toxic iron bisglycinate form

- Existing models completely ignore any consideration of the benefits of nutrients, and result, in many cases, in the exclusion of beneficial levels of nutrients

- Risk assessments conducted to-date use selected studies and have ignored key scientific studies in peer-reviewed journals

- The Federal Institute of Risk Assessment (BfR) have used these methods and have provided maximum daily levels of vitamins and minerals that are viewed as excessively low by most clinical nutritionists, e.g. 225 mg of vitamin C, 15 mg of vitamin E, 5.4 mg of vitamin B6 and 5 mcg of vitamin D3. See Tables 1 and 2 below for data on SULs and the BfR MPLs.

If this same two-stage approach were used in other areas of food law, we would see bans on foods as commonplace as peanuts, dairy and wheat products!

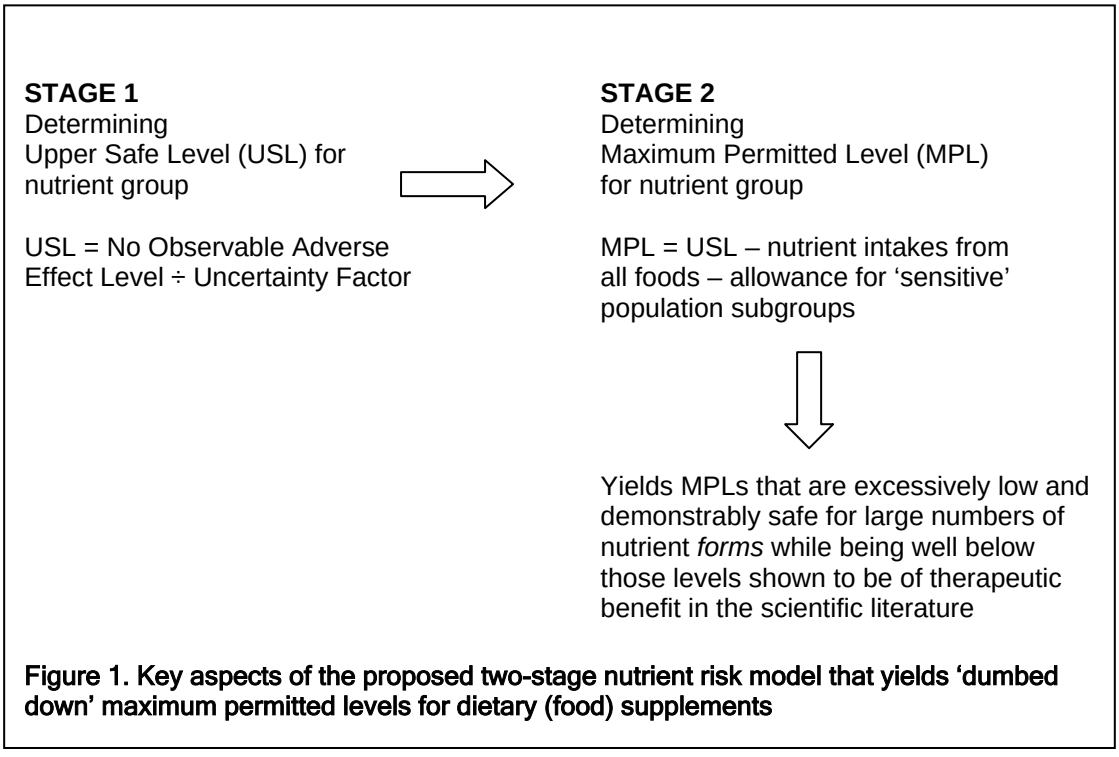

Figure 1. Key aspects of the proposed two-stage nutrient risk model that yields 'dumbed down' maximum permitted levels for dietary (food) supplements

What does the BfR model do to nutrient 'maximum permitted levels'?

The best way of testing or validating a model is to evaluate outputs after inputting real data. The BfR, to our knowledge, is the only organisation yet to have undertaken this task and these levels are summarised in the right-most column of the following Tables.

Table 1. Vitamin SULs and MPLs

Vitamin	Upper Safe Levels			Maximum Permitted Levels
	USA (Food & Nutrition Board)	EU (European Food Safety Authority)	UK (Expert Group on Vitamins and Minerals)	Germany (BfR)
Vitamin A (mcg)	3000	3000	1500	800
Beta carotene (mg)	Not set (for smokers)	Not set (for smokers)	7 mg (0 mg for smokers)	4
Vitamin C (mg)	2000		1000	225
Vitamin D (mcg)	50	50	25	5
Vitamin E (mg)	1000	300	540 (800 IU)	15
Vitamin K (mcg)	Not set	Not set	1000	80
Vitamin B1 (mg)	Not set	Not set	100	1.3
Vitamin B2 (mg)	Not set	Not set	40	4.5
Niacin (B3) (mg)	35	900	500	17
Vitamin B6 (mg)	100	25	10	5.4
Folic acid (B9) (mcg)	1000	1000	1000	400
Vitamin B12 (mcg)	Not set	Not set	2000	9
Pantothenic acid (mg)	Not set	Not set	200	18
Biotin (mcg)	Not set	Not set	900	180

Table 2. Mineral SULs and MPLs

Mineral	Upper Safe Levels			Maximum Permitted Levels
	USA (Food & Nutrition Board)	EU (European Food Safety Authority)	UK (Expert Group on Vitamins and Minerals)	Germany (BfR)
Potassium (mg)	Not set	Not set	3700 (suppl)	2000
Calcium (mg)	2500 (total)	2500 (total)	1500 (suppl)	1200
Phosphorus (mg)	4000	Not set	250 (suppl)	1250
Magnesium (mg)	350	250	400	400
Iron (mg)	45	Not set	17	15
Iodine (mcg)	1100	600	500	200
Fluoride (mg)	10	Not set	Not set	3.8
Zinc (mg)	40	25	25	10
Selenium (mcg)	400	300	200	70
Copper (mg)	10	5	10	1.5
Manganese (mg)	11	Not set	4	5
Chromium (mcg)	Not set	Not set	10,000	100
Molybdenum (mcg)	2,000	600	0 (suppl) 230 (diet)	100

These MPLs would, in the view of ANH, decimate nutritional therapy as we know it. Applied to non-vitamin and mineral ingredients such as essential fatty acids, amino acids and phytonutrients, the results would likely be even more catastrophic.

Misapplication of the precautionary principle

At the heart of all this scientific irrationality is a principle that has absolutely nothing whatsoever to do with pure science. It is the 'precautionary principle' that first came to the fore, belatedly yet aptly, with the Rio

Declaration on Environment and Development in 1992 with the laudable objective of protecting the environment, in the face of scientific uncertainty.

The precautionary principle, in this context, states:

> *"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."*[2]

When the European Food Safety Authority was established in 2002 under an EU Regulation, the Rio Declaration, intended for the protection of the environment, was transposed to health policy in the European Union. Unfortunately, its applicability to EU food supplement law was firmly clarified by the European Court of Justice, in its ruling on the Alliance for Natural Health's case challenging EU-wide bans on food supplements.

The precautionary principle has been misapplied to health policy and food supplement law in Europe and now may provide one of the greatest obstacles to freedom of choice in healthcare. This problem is demonstrated clearly in a recent paper published by Dr Jaap Hanekamp of the HAN Foundation in the peer reviewed journal *Environmental Liability*.[3]

ANH strategy on risk assessment

There are a number of key strands in the ANH strategy in this area. These are summarised below:

- Working to re-shape existing methodologies to take into account:
  - Categorisation of risk/benefit assessment by nutrient forms, rather than by nutrient groups
  - Consideration of benefits in assessments
  - Development of a tiered/prioritised system for risk/benefit assessments
  - Avoiding misuse of the precautionary principle as a means of ensuring that significant sectors of the population are not excluded access to beneficial nutrient forms and dosages
  - Use of all available published data in assessments via specified, broad inclusion criteria
  - The inclusion of observational and clinical data where appropriate to assist in the development of more complete dose/response data
- Exposing in peer reviewed journals the flawed nature of existing nutrient risk assessment models
- Establishing a post-doctoral research project to develop a new, scientifically rational model
- Disseminating the new model as widely as possible, encouraging uptake by regulatory authorities at all levels

The ANH is working on these tasks collaboratively with a risk assessment institute in the Netherlands, the HAN Foundation, as well as with other scientists.

A call for action

Any companies who would like to be more directly involved in this issue, taking the exemplary lead of the International Nutrition Company in the Netherlands, should contact us at your earliest convenience. Please email our Development Manager, Meleni Aldridge, at mel@anhcampaign.org or telephone +44 (0)1306 646 551.

---

[2] See Principle 15: http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm

[3] Hanekamp H, The precautionary principle: a critique in the context of the Food Supplements Directive. *Environmental Liability*, 2002, 2: 43-51. The article can be downloaded from: http://www.alliance-natural-health.org/_docs/ANHwebsiteDoc_239.pdf).

USA

Latest update on AER Bill

Source: Lee Bechtel, Bechtel & Associates. Lobbyist to American Association for Health Freedom, ANH Affiliate.

Several changes were made from the original bill. The following adds some clarification, based on the stated Congressional intent, if or when a similar AER bill is enacted by the House and Senate in the future, as currently pending before the Senate.

Implementing Guidance-Regulations

". . . . Includes a provision requiring the Secretary of Health and Human Services to issue guidance on the minimum data elements that should be included in any serious adverse event reports submitted..."...."it is the committee's strong view that the industries affected by S. 3546 should undertake as quickly as possible training for their staff so that they are aware of their surveillance, investigation and reporting duties."

Analysis - Both guidance documents and regulations will be open to public comment. There are specific time lines, if and when legislation is enacted, for revising the MedWatch reporting form. Specific reference is made to drug interactions, etc.

Job Opportunity for CAM Doctors

"... The committee is aware of concerns that parties responsible for reporting have expressed they may not have the expertise to determine if an adverse event falls within the definition of "serious". The committee recognizes that many manufacturers have indicated they will contract their reporting function to a third party which has greater medical expertise. S. 3546 allows such contracting, with the understanding that the manufacturer, packer or distributor still maintains ultimate responsibility for reporting under the law."

Analysis - This would be a cost to all sizes of manufacturers, packers, or distributors who have reporting responsibility. Who would most benefit from professional expertise, after the issuance of guidance from the FDA? Regardless of a direct medical causality related to a supplement, an AER must still be filed. But see below.

Reporting AER and new "medical or supplemental information" that would negate the credibility of a filed AER

"Due to concerns expressed by reporting parties about the significant burden posed by this ongoing requirement, S. 3546 as approved by the committee limits this responsibility so that the manufacturer, packer or distributor must only report additional information received within 1 year of the initial report. The committee notes that the application of this provision is limited to reports of additional medical information the responsible person receives from an individual reporter or person acting on behalf of the reporter. Material related to litigation about the event does not fall within the scope of this reporting requirement....In the committee's view, new medical information or supplemental information that is submitted should become part of the original report, including information that would either bolster or negate the credibility of the initial report."

Analysis - AER reporting is not just a one way street. People like Dr. Lieberman could also be in demand, as current or new scientific published studies are done which address issues directly related to a filed AER. Or, a CAM doctor hired as an outside consultant, could also file counter scientific studies with an AER. A report fits the mandatory data filing requirements, a supplement may be a cause of a serious medical outcome, but other medical information suggests that it may not be? People focus on the negative aspects of reporting, but this provision also opens the door for having more professional opinions - doctors, and studies included in the body of evidence retained by the FDA on the safety of supplements/ingredients.

"...retailers who do not have such private label products, that is, products bearing the retailer's name, do not have any reporting obligation under S. 3546. Retailers who have private label products will have to make a decision about who will be the responsible person for the purposes of reporting. Such retailers will have to choose either to assign the reporting responsibility by agreement to the manufacturer of their private label

products, or report the serious adverse events themselves."

Analysis - Business relationships will be redefined. Retailer private labeling would most likely disappear, but they could still sell products under a manufacturer's label.

Homeopathic and Chinese Medicines

The committee is aware that some have suggested "homeopathic remedies" and "traditional Chinese medicines" should be included in the mandatory reporting system required by S. 3546. The committee believes there is no need for an explicit inclusion of homeopathic remedies in this legislation. …There is no explicit reference to "Traditional Chinese Medicines," or as they are sometimes called "Traditional Asian Medicines," in Federal food and drug law. However, herbal products that are used in traditional Chinese medicine and that are marketed as supplements would be covered by S. 3546."

Importation of Supplement Ingredients or Finished Products

During the drafting of S. 3546, three concerns were raised about the Food and Drug Administration's ability to take action against imported products if the foreign manufacturer were not in compliance with the reporting requirements of this act. The current section 801 of the FFDCA is inadequate to address this situation…. The new section 5 of S. 3546 added with the substitute approved by the committee will address this situation. The first concern relates to a case in which a foreign manufacturer's product arrives at port and does not properly contain the name and contact information on the label. That case is addressed by the provisions of S. 3546 stating that the label must contain and name and address or telephone number or else it is misbranded. In that case, the FDA has authority to refuse admission... The second concern is whether the language amending section 801 in S. 3546 applies to finished products only, or whether it includes raw materials. Because the plain language of the bill refers to an "article that is subject to a requirement under section 760 or 761," it is clear that it applies only to finished products and not raw materials or dietary ingredients, which are not subject to section 760 or 761. The third instance, in which the imported product itself may appear to comply with the law, but the manufacturer has not filed adverse event reports in the past, for this or other products… Section 5 amends section 801 of the FFDCA so that an imported OTC drug or a dietary supplement shall be refused admission if the FDA has credible information indicating that the responsible person has not complied with its reporting responsibilities. To rectify this situation, the responsible person, or the owner or consignee on behalf of the responsible person, may seek authorization to act to ensure that he is in compliance. If FDA grants the application, it will authorize the applicant to perform the actions specified in the authorization upon the filing of a bond, under the supervision of an officer or employee of the FDA. There is no requirement in this legislation that the FDA certify for compliance each import admitted into this country under section 801."

Analysis - US distributors of supplements manufactured by a foreign manufacturer will have to "register" and report with the FDA, depending upon whether a product is a finished or raw product. See above. So, in effect, they would incur the cost, or get reimbursed for the cost of FDA compliance, from their foreign manufacturer, which levels the cost field with US manufacturers and distributors. Yes, big companies, NNFA companies, would have a cost advantage compared to smaller supplement only companies that manufacturer supplements. However, market dynamics would change. One could expect that small manufacturers and distributors could share in the reporting costs, or not? Consumer, retailer, physician costs would go up more for products made by small companies. Which ways the profit margins go would be market driven.

Exceptions

It is expected that supplements composed only of vitamins and minerals would be exempted from reporting. The HHS/FDA is granted authority to do this. An implementation issue, if and when enacted into law.

For further information about the ANH,
the ANH Innovators Club or ANH Consultancy Ltd,
please contact:

Meleni Aldridge
Development Manager
Alliance for Natural Health
Tel: +44 (0)1306 646 550
Email: mel@anhcampaign.org