

Summary of Responses to the 2 March 2005 Consultation on The Tryptophan in Food (England) Regulations 2005 (“the draft Regulations”)

Responses requested on:

1. The potential market for L-tryptophan-containing food supplements
2. The impact on comparable products of introducing L-tryptophan-containing food supplements on to the market.
3. The impact on producers of introducing purity criteria for L-tryptophan-containing products for particular nutritional uses.

RESPONDENTS TO THE FSA CONSULTATION EXERCISE ON THE TRYPTOPHAN IN FOOD (ENGLAND)
REGULATIONS 2005 (“THE DRAFT REGULATIONS”)

| Respondent | Abbreviation |
|---|---------------------|
| Kraeber | KRA |
| Dr Kingsley | DrK |
| Margaret Moss | MaM |
| Health Food Manufacturers' Association | HFMA |
| Institute for Optimum Nutrition | ION |
| The National Pharmaceutical Association | NPA |

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REGULATIONS 2005 (“THE DRAFT REGULATIONS”).

Please note that this table is a summary and is not meant to be exhaustive.

| Respondent | Comment | FSA Response |
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| KRA | <ol style="list-style-type: none"> 1. It is very important that the correct form of tryptophan is used and the correct purity as tryptophan (not L-tryptophan) could be a health risk. 2. Test methods for purity should be accurate and validated as this would be an assurance to suppliers of supplements and consumers that the raw materials had been checked by an accredited laboratory. | The purity criteria that must be complied with, is that set by the European Pharmacopoeia. |
| DrK | <ol style="list-style-type: none"> 1. L-tryptophan is an essential amino acid in many respects and is, in particular important as a precursor for the natural production of serotonin, which is an important neurotransmitter. 2. Concern that when people take current amino acid supplements there is an imbalance due to lack of Tryptophan. 3. The ban on tryptophan should be lifted so that providers of amino acid supplements can include L-tryptophan in the complete formula and that the formula itself remains balanced. | Comments noted. The previous regulations prohibiting the use of tryptophan have been revised to allow L-tryptophan back onto the market. |

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| MaM | <ol style="list-style-type: none"> 1. The potential market depends on whether 220mg is enough as doctors in Princeton use amino acids at 500mg as a minimum with adults. If not people will continue to use alternatives like 5-hydroxytryptophan. 2. Insomnia sufferers or those suffering from depression may welcome L-tryptophan as a natural alternative to SSRI drugs or addicts to these drugs may use L-tryptophan to help discontinue their use. 3. People may find 220mg adequate if taken together with nutrients involved in converting L-tryptophan to serotonin. People will need to seek advice on this. There may be a market for this type of combined supplement but companies would need to seek advice, as they don't have the expertise to formulate this type of supplement. 4. The impact on comparable products will depend on the whether 220mg is effective, it also depends on cost which partly depends on cost of checking purity. Purity testing will be a cost to producers but may be offset by increased sales. 5. Welcome proposed re-introduction of L-tryptophan and the purity criteria to avoid the recurrence of the eosinophilia-myalgia syndrome (EMS) tragedy. 6. Hope that human studies will be carried out to find out if a level of 500mg or 1g is safe. | <p>The recommended daily allowance of 220mg/day was set following a review by the COT; in their opinion this level does not present an appreciable risk to human health. The COT will be reviewing its recommendation, and any new evidence that has come to light at its meeting in December. The regulations may be amended depending on the outcome of these discussions.</p> <p>Comments noted</p> <p>Comments noted. See response to point 1.</p> <p>Comments noted</p> <p>Comments noted</p> <p>Comments noted</p> |
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| <p>HFMA</p> | <p>1. Whilst welcoming the proposed rescinding of the ban on the use of L-tryptophan in supplements we urge that the COT be asked to review again the recommended SUL of 220mg as that level is extraordinarily cautious. This level will also limit the potential benefit of supplementation for the consumer and inhibit commercial benefit or re-releasing L-tryptophan for use in food supplements.</p> <p><u>Meeting Purity Criteria</u></p> <p>2. Meeting the purity criteria seems unlikely to be a major issue for material or finished goods suppliers.</p> <p><u>Potential Marketplace Implications</u></p> <p>3. Since it is 15 years since L-tryptophan food supplements were available it will at best take some time to re-build consumer sales. An HFMA questionnaire was issued to companies seeking sales estimates for L-tryptophan. Sales prospects are highly sensitive to the maximum potency allowed – sales for 5 companies questioned will total £140k assuming the COT MPL of 220mg; a further £265k would be added if the MPL matched the level in the Netherlands (600mg); and this would increase by £710k if the MPL were to be 1000mg. On average, half the sales for the companies would be incremental. Sales will be evenly balanced between use in single-nutrient supplements and multiple formulas. The modest impact of sales of L-tryptophan supplements on existing products will be diffuse.</p> | <p>Comments noted. The recommended daily allowance of 220mg/day was set following a review by the COT; in their opinion this level does not present an appreciable risk to human health. The COT will be reviewing its recommendation, and any new evidence that has come to light at its meeting in December. The regulations may be amended depending on the outcome of these discussions.</p> <p>Comment noted</p> <p>Comments noted. This information has been included in the Regulatory Impact Assessment. See point 1 above regarding COT recommendation.</p> |
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| | <p><u>Safe Upper Limit</u></p> <p>4. Fully endorse the scientific arguments presented in the submission. We would emphasise however that the COT state that it was likely that L-tryptophan per se was not causal for EMS but that EMS was due to one or more contaminants. Also the application of an uncertainty factor of 10 to the mean therapeutic dose seems arbitrary on both counts given that it results in a max daily intake that is less than 5% LOAEL and below the 2 estimates of the average tryptophan requirements in adults.</p> <p><u>Proposal</u></p> <p>5. The maximum daily intake, and maximum potency per supplements, be set at 1000mg and that all L-tryptophan supplements carry the following advisory statement “Take [L-tryptophan food supplements] with food. Do not use of you are taking anti-depressant medicine unless under the supervision of your doctor”. When appropriately framed, we think the legislation should be enacted with maximum speed.</p> | <p>COT recognised that there are some uncertainties and that it cannot be entirely ruled out that the apparent epidemic may have been due to the increased use of L-tryptophan supplements and the recognition of EMS. Therefore, reintroduction of L-tryptophan supplements at 220mg/day was recommended by COT as not presenting an appreciable risk to health.</p> <p>See point 2 above.</p> <p>The regulations allow L-tryptophan at a level of 220mg.day. The severity of the symptoms of EMS and the uncertainty relating to gaps in the scientific evidence, led to the setting of a daily dose level that would not present an appreciable risk to health rather than the use of advisory statements. See also response to point 1.</p> |
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| <p>ION</p> | <ol style="list-style-type: none"> 1. The ban on the inclusion of the essential amino acid tryptophan in food supplements should be rescinded, together with implementing purity criteria controls to avoid further risk of contaminated product reaching the public. 2. We do not agree that an upper limit for tryptophan in food supplements should be made on the basis of 'applying an uncertainty factor of 10 to the mean therapeutic dose of 2228mg of tryptophan per day', as recommended in the current draft regulation. The Safe Upper Level (SUL) of tryptophan allowed in supplements should be determined on the same basis as any other nutrient. The SUL should also take into consideration the optimal daily requirement for tryptophan and should, by definition, not be lower than the optimal daily requirement. The EVM report states "Nutritional need was taken into account to ensure that Safe Upper Levels were not set at a level below dietary requirements. There is insufficient data to conclusively set a Safe Upper Level due to the lack of long-term studies, however all the clinical trials to date, and there have been many, indicate that tryptophan supplementation up to a level of 6,000 mg per day, does not induce significant adverse effects (drowsiness, mild nausea if taken without food), all of which cease within hours of cessation of supplementation. No long-term studies of large amounts have been carried out. However, what is known about the biochemical dynamics of tryptophan does not predict an accumulative toxicity at such amounts. Recommend that a suggested Safe Upper Level for tryptophan based on existing data be set at 1,666mg, by applying an Uncertainty Factor of 3 to the LOAEL of 5,000mg. In practical terms supplements are unlikely to contain more than 1,000mg due to the volume in a capsule/tablet. This amount was also the most common amount per capsule/tablet available prior to 1990. | <p>Comment noted. The previous regulations have been revised to allow tryptophan back onto the market.</p> <p>The recommended daily allowance of 220mg/day was set following a review by the COT, this review included consideration of the nutritional needs for L-tryptophan and the scientific studies on EMS and L-tryptophan supplementation. In the COT's opinion this level does not present an appreciable risk to human health.</p> <p>The Expert Group on Vitamins and Minerals (EVM) proposed Safe Upper Levels (SULs) for vitamins and minerals using the well-established paradigm for setting acceptable and tolerable intake levels for chemicals in food. This involves identifying hazards, characterising the dose-response relationship to identify a NOAEL or LOAEL and applying uncertainty factors to allow for inter- and intra-species variability and for missing information. Where the data were not adequate to set a SUL, the EVM gave guidance on levels that would not be expected to result in adverse effects.</p> <p>The COT uses the same paradigm. In its evaluation of tryptophan, the COT noted significant uncertainties. Although the COT did not use the EVM terminology, it is clear that the data did not support derivation of an SUL, and the COT conclusion is expressed in the same terms that EVM used for its guidance levels. The therapeutic use of tryptophan was the only available basis for the safety assessment. The COT decided that an uncertainty factor of 10 should be applied to derive a dose that would not be expected to be a risk to health in the general population. This factor is for uncertainty related to the gaps in the scientific evidence. The COT secretariat has reviewed the further evidence submitted and is of the opinion that this does not constitute any new evidence. However, the COT will be reviewing its recommendation and considering any new evidence, which has come to light at its December meeting.</p> |
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| NPA | 1. Support the prohibition of the addition of L-tryptophan to food, and the sale, offer for sale and exposure for sale of food containing tryptophan subject to exceptions. We support the amendment of the regulations to allow tryptophan to be added to food supplements provided that the added tryptophan complies with purity criteria and provided that the recommended daily dose does not exceed 220mg. Community pharmacists are well placed to advise customers on the safe use of supplements containing tryptophan. | Comments noted. The regulations have been amended to allow the use of L-tryptophan at a level of 220mg/day, and providing it meets the necessary purity criteria set by the European Pharmacopoeia. |
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