European Food Safety Authority

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SCIENTIFIC OPINION

Inositol hexanicotinate (inositol hexaniacinate) as a source of niacin (vitamin B_3) added for nutritional purposes in food supplements [1]

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (ANS)

(Question No EFSA-Q-2005-213, EFSA-Q-2006-199)

Adopted on 29 January 2009

This opinion replaces the earlier version published on 13 February 2009.[2]

PANEL MEMBERS

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SUMMARY

Following a request from the Commission to the European Food Safety Authority, the Scientific Panel on Additives and Nutrient Sources added to Food was asked to provide a scientific opinion on the safety of inositol hexanicotinate (inositol hexaniacinate) added for nutritional purposes as a source of niacin (vitamin B_3) in food supplements and on the bioavailability of nicotinic acid from this source.

The present opinion deals only with the safety of inositol hexanicotinate as a source of nicotinic acid, one of the vitamers of niacin (vitamin B_3), intended for the general population, to be added to food supplements and the bioavailability of nicotinic acid from this source. The safety of nicotinic acid itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on inositol hexanicotinate (inositol hexaniacinate) as a source for niacin (vitamin B_3) added for nutritional purposes in food supplements following a request from the European Commission. *The EFSA Journal* (2009) 949, 1-20.

[2] Editorial changes – page 11 and 16 – reference metabolites : Chang and Johnson, 1961; Abelson *et al.,* 1963; Eitenmiller, 2007 was inserted. The changes do not affect the overall conclusion of the opinion. To avoid confusion, the original version has been removed from the website.

The petitioner indicates that inositol hexanicotinate is, at least in part, absorbed intact and hydrolysed in the body, releasing free nicotinic acid and inositol. Gastrointestinal absorption of inositol hexanicotinate varies widely, with an average of 70% of an orally ingested dose absorbed into the bloodstream.

When inositol hexanicotinate is administered orally to humans, this results in a sustained increase in the level of free nicotinic acid in blood and plasma. Inositol hexanicotinate appears to be metabolised slowly, not reaching maximum serum levels of nicotinic acid until approximately 6-10 hours after ingestion, whereas upon intake of free nicotinic acid plasma levels peak after 0.5-1 hour.

From the various studies reported, the Panel concludes that nicotinate from inositol hexanicotinate is bioavailable and a source of niacin.

The safety of nicotinic acid has been evaluated by various authorities including the Scientific Committee on Food (SCF).

In 2002, the SCF established a Tolerable Upper Intake Level for nicotinic acid of 10 mg/day using a point of departure of 30 mg/day, at which dose level occasional flushing, the limiting adverse effect, had been reported. An uncertainty factor of 3 was applied to allow for the fact that a slight effect was reported, and that the study was performed in a small number of subjects, but taking into account the steep dose-response relationship. The Panel noted that the UL established by the SCF did not apply to pregnant and lactating women.

Furthermore the Expert Group on Vitamins and Minerals (EVM) has established that a dose of 17 mg nicotinic acid/day, for supplementation only, would not be expected to have any significant adverse effects.

One petitioner indicates an anticipated use of inositol hexanicotinate in food supplements up to 495 mg inositol hexanicotinate/day providing 450 mg nicotinic acid /day, whereas a second petitioner indicates that the source is intended to be used in food supplements at levels providing 40 mg inositol hexanicotinate/day which corresponds to 36.4 mg/day nicotinic acid and 8.8 mg/day inositol.

The Panel notes that these proposed use levels of inositol hexanicotinate provide levels of nicotinic acid that are 4 to 45 times higher than the Tolerable Upper Intake Level for nicotinic acid of 10 mg/day set by the SCF.

No genotoxicity data are available on inositol hexanicotinate. However, as inositol hexanicotinate is hydrolysed to inositol and nicotinic acid, which are endogenous compounds and occur in several dietary products as well, the Panel concluded that the absence of genotoxicity data does not raise any concern.

The petitioners indicate that inositol hexanicotinate acts as a slow-release supply of nicotinic acid and that therefore, the flushing effect is not likely to occur when inositol hexanicotinate is used as a source of niacin since the nicotinic acid molecules slowly hydrolyse from the inositol.

The Panel notes that given the slow release of nicotinic acid from inositol hexanicotinate, the flushing effect, on the basis of which both the SCF and EVM have given Tolerable Upper Intake Levels for nicotinic acid, may be conservative for inositol hexanicotinate. However, given the absence of studies adequately supporting the absence of a flushing effect when dosing inositol hexanicotinate, the Panel concludes that the upper limit for nicotinic acid of 10 mg/day should also be used to judge the safety of inositol hexanicotinate.

A daily dose of 10 mg nicotinic acid given as inositol hexanicotinate would amount to a daily dose of 11 mg inositol hexanicotinate, resulting in release of 2.4 mg inositol upon hydrolysis.

Given the estimated normal dietary intake of inositol that amounts to 335-1500 mg myo-inositol (the most important form of naturally occurring inositol)/day, the Panel concludes that the intake of 2.4 mg inositol/day, resulting from intake of inositol hexanicotinate at a level that corresponds to a daily dose of 10 mg nicotinic acid, would not be of safety concern.

The Panel concludes that the use of inositol hexanicotinate as a source for niacin, when added for nutritional purposes in food supplements intended for the general population, would be of no safety concern provided that use levels are in compliance with the defined upper safe use level for nicotinic acid (10 mg/day).

However, the Panel is concerned that the use levels of inositol hexanicotinate proposed by the petitioners are 40 and 495 mg/day providing 36.4 and 450 mg nicotinic acid/day. These proposed use levels provide levels of nicotinic acid that are 4 to 45 times higher than the Tolerable Upper Intake Level of 10 mg nicotinic acid/day defined by the SCF in 2002.

Key words:

Food supplements, niacin, nicotinic acid, vitamin B_3, inositol hexanicotinate, inositol hexaniacinate, CAS Registry Number 6556-11-2.

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BACKGROUND AS PROVIDED BY THE COMMISSION

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of inositol hexanicotinate (inositol hexaniacinate) added for nutritional purposes to food supplements. The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements[3].

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of inositol hexanicotinate (inositol hexaniacinate) added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group B on Food Additives and Nutrient Sources for the preparation of this opinion: D. Boskou, U.R. Charrondiere, B. Dusemund, D. Gott, T. Hallas-Møller, K.F.A.M. Hulshof, J. König, D. Parent-Massin, I.M.C.M. Rietjens, G.J.A. Speijers, P. Tobback, T. Verguieva, R.A. Woutersen.

[3] OJ L 183, 12.7.2002, p.51.

ASSESSMENT

1. Introduction

The present opinion deals only with the safety and bioavailability of inositol hexanicotinate (inositol hexaniacinate) as a source of nicotinic acid, one of the vitamers of niacin (vitamin B_3) to be added to food supplements intended for the general population. The safety of nicotinic acid itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

Niacin is the precursor for two cofactors; NAD^+ (nicotinamide adenine dinucleotide) and $NADP^+$ (nicotinamide adenine dinucleotide phosphate), both of which are essential for the functioning of a wide range of enzymes involved in redox reactions. In addition, NAD^+ is the source for ADP-ribose, which is used in repairing DNA breakage caused by mutagens and other toxins.

2. Technical data

2.1. Chemistry

Inositol hexanicotinate

The CAS number for inositol hexanicotinate is 6556-11-2. Synonyms are hexanicotinoyl inositol, hexopal, inositol (hexa)nicotinate, mesoinositol hexanicotinate, hexanicotol, myo-inositol, hexa-3-pyridinecarboxylate, nicotinic acid hexaester with myo-inositol, 3-pyridinecarboxylic acid, 1,2,3,4,5,6-cyclohexanehexayl ester, inositol hexaniacinate, meso-inositol hexanicotinate and myo-inositol hexanicotinate.

The molecular formula of inositol hexanicotinate is $C_{42}H_{30}N_6O_{12}$, its molecular weight is 810.7 g/mol and its structural formula is presented in Figure 1.

Hydrolysis of 1 g (1.23 mmol) inositol hexanicotinate provides 0.91 g nicotinic acid and 0.22 g inositol.

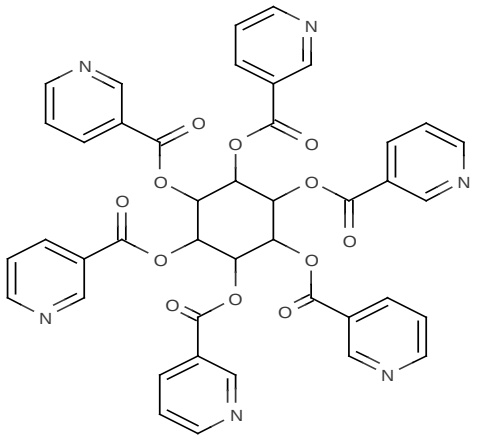

Figure 1. **Molecular structure of inositol hexanicotinate**

Inositol hexanicotinate is to be used as a source of niacin in food supplements. Niacin (Figure 2) is the generic term for both nicotinic acid and nicotinamide.

Figure 2. **Molecular structure of nicotinic acid and nicotinamide both considered vitamers of niacin (Vitamin B_3).**

2.2. Specifications

Inositol hexanicotinate

There were two petitioners for inositol hexanicotinate.

The first petitioner indicated that inositol hexanicotinate is a white or almost white crystalline powder that is insoluble in water, ethanol, acetone and ether, slightly soluble in chloroform and soluble in dilute mineral acids. The purity is not less than 98.0% and adequate specifications for heavy metals were not provided, whereas chloride is not more than 350 mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of lead, mercury and cadmium, in food supplements as sold, should be 3.0 mg/kg, 0.1 mg/kg and 1.0 mg/kg, respectively.

The second petitioner indicated that inositol hexanicotinate is a white to almost white powder, almost odourless, practically insoluble in water, sparingly soluble in chloroform, and practically insoluble in acetone, ethanol and ether. It dissolves in dilute mineral acids. Heavy metals are not more than 10 mg/kg, chloride not more than 100 mg/kg, acetone not more than 0.5%, loss on drying 0.5% max and residue on ignition 0.1% max.

2.3. Manufacturing Process

Inositol hexanicotinate

Inositol hexanicotinate is produced by chemical synthesis from inositol and nicotinic acid.

2.4. Methods of analysis in food

Inositol hexanicotinate

Inositol hexanicotinate is hydrolysed to inositol and six molecules of nicotinic acid. Following breakdown to inositol and nicotinic acid, the latter may be determined by the König reaction or by a microbiological assay with *Lactobacillus plantarum*.

Other techniques include UV spectrophotometry, colorimetry, titrimetric and gas chromatography.

2.5. Reaction and fate in foods to which the source is added

Inositol hexanicotinate

One petitioner indicates that inositol hexanicotinate is relatively stable in food supplements. The second petitioner indicates that inositol hexanicotinate has a shelf-life of 3 years, but no supporting data were provided.

2.6. Case of need

Inositol hexanicotinate

Inositol hexanicotinate is to be used as a source of niacin in food supplements. One petitioner indicates that inositol hexanicotinate is used by food supplement manufacturers as an ingredient in tablets, caplets, capsules, chewable tablets, effervescent powders and liquids that are food supplements. The method of incorporation is determined by the individual manufacturers as appropriate for the particular types of finished products. The petitioner also indicates that normally levels of niacin in food supplements are restricted by the resulting 'flushing reaction' in consumers after intake of levels >20mg. The UK food supplements industry has agreed with the UK Food Standards Agency (FSA) that products containing more than 20 mg of niacin should carry the following advisory statement: "This amount of nicotinic acid may cause skin flushes in sensitive individuals". The term flushing covers a burning, tingling and itching sensation as well as a reddened flush on the face, as well as on arms and chest.

Inositol hexanicotinate acts as a slow-release supply of nicotinic acid as the molecule breaks down into inositol and the six nicotinic acid molecules. The petitioner states that the flushing effect is not likely to occur when inositol hexanicotinate is used as a source of niacin since the nicotinic acid molecules slowly dissociate from the inositol.

One petitioner indicated that intake recommendations for inositol hexanicotinate would be consistent with those advised for nicotinamide preparations of up to 450 mg/day of nicotinic acid. The amount of 450 mg nicotinic acid will be provided by 495 mg inositol hexanicotinate delivering upon hydrolysis also 108 mg inositol.

The second petitioner for inositol hexanicotinate indicates that inositol hexanicotinate combines the properties of both nicotinic acid and inositol in a single ingredient, without any flushing effects. The petitioner indicates that the source is intended to be used in food supplements, i.e. in capsules, tablets, ampoules or powders at the proposed use level of 40 mg

inositol hexanicotinate/day. Hydrolysis of 40 mg inositol hexanicotinate results in 36.4 mg nicotinic acid and 8.8 mg inositol.

2.7. Information on existing authorisations and evaluations

2.7.1. Nicotinic acid

Nicotinic acid is listed in Directive 2002/46/EC (2002), as amended, as a permitted source of niacin.

Because of the metabolic formation of niacin from tryptophan, the dietary requirements for niacin are complex relating to the dietary content of both tryptophan and niacin. By convention the total niacin equivalents in the diet are calculated as the sum of preformed niacin (i.e. nicotinic acid plus nicotinamide) plus 1/60 of the tryptophan content. There is no absolute requirement for preformed niacin in the diet, and the SCF evaluation recommended intakes of niacin equivalents between 9 and 18 mg/day (SCF, 1993). In 2002, the SCF in its Opinion on the Tolerable Upper Intake Levels of nicotinic Acid and nicotinamide (niacin) concluded that it is likely that there is no requirement for any preformed niacin in the diet under normal conditions and that endogenous synthesis from tryptophan will meet requirements.

The SCF has established a Tolerable Upper Intake Level (UL) for nicotinic acid of 10 mg/day, using a point of departure of 30 mg/day, at which dose level occasional flushing, the limiting adverse effect, had been reported. An uncertainty factor (UF) of 3 was applied to allow for the fact that a slight effect was reported, and that the study was performed in a small number of subjects, but taking into account the steep dose-response relationship (SCF, 2002).

The SCF indicated that the UL of 10 mg/day for free nicotinic acid is not applicable during pregnancy or lactation because of inadequate data relating to this critical life stage. The ULs for children and adolescents have been derived on the basis of their body weights.

The Expert Group on Vitamins and Minerals (EVM) has not established a UL for nicotinic acid, due to insufficient data. For guidance purposes, a factor of 3 is used based on a LOAEL of 50 mg/day due to the absence of a NOAEL. Thus, a dose of 17 mg nicotinic acid/day, for supplementation only, would not be expected to have any significant adverse effects. The dose is equivalent to 0.28 mg/kg bw/day in a 60 kg adult. This guidance level is given for supplements only, as adverse effects appear to be related to acute, bolus intakes of nicotinic acid rather than more sustained exposure as would occur with ingestion of nicotinic acid via food (EVM, 2003).

In the UK there is mandatory fortification of flour (except wholemeal and certain other specified types) with nicotinic acid at a level of not less than 1.6 mg/100 g flour for restoration purposes (EVM, 2003).

Inositol

Inositol is listed in Directive 2001/15/EC (EC, 2001), as amended, as a dietary food for particular nutritional uses (FPNU). These include foods for particular nutritional uses, intended for special medical purposes (FSMPs), but exclude infant and follow-on formulae, processed cereal-based foods and baby foods intended for infants and young children.

Inositol is listed by the US Food and Drug Administration (FDA) as substances 'Generally regarded as safe' (GRAS), (FDA, 2004).

Inositol hexanicotinate

Inositol hexanicotinate was in use as an ingredient in food supplement products legally on sale in the UK in 2002.

2.8. Exposure

Free nicotinic acid and nicotinamide are present in nature in only small amounts. Nicotinic acid is mainly bound to macromolecules in plants, while nicotinamide is usually a component of NADP in the animal world. Important sources of preformed niacin include beef, pork, wheat flour, maize (corn) flour, eggs and cows' milk. Human milk contains a higher concentration of niacin than cows' milk (EVM, 2003). In unprepared foods, niacin is present mainly in the form of the cellular pyridine nucleotides NAD and NADP. Enzymatic hydrolysis of the co-enzymes can occur during the course of food preparation. Boiling releases most of the total niacin present in sweet corn as nicotinamide (up to 55 mg/kg) but very little as nicotinic acid (<5 mg/kg). The niacin in cereals such as wheat, barley and oats does not result in free nicotinic acid or nicotinamide on cooking. Roasted coffee contains higher concentrations of free nicotinic acid (160-400 mg/kg) (SCF, 2002).

According to the SCF (2003), mean intakes of niacin equivalents in European adults ranged from about 12 to 40 mg/day. At the 97.5th percentile, the intake amounts up to 63 mg/day, from food sources only, and to 67 mg/day from food sources plus supplements.

Inositol hexanicotinate

The petitioner reports that inositol hexanicotinate as such is not reported to be found in nature or natural products in appreciable amounts. The Panel notes that *myo*-inositol (*cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol) is the most prominent naturally occurring form of inositol with fruit, beans, grains and nuts being the main sources. The estimated dietary intake of myo-inositol (the most important form of naturally occurring inositol) ranged from 335-1500 mg/day (Clemens and Darnell, 1980).

The petitioner indicates that the anticipated exposure of the population to inositol hexanicotinate in food supplements is either by self-selection of products containing multivitamins and multiminerals, or as more specific combinations, containing inositol hexanicotinate providing up to 450 mg/day of nicotinic acid. The amount of 450 mg nicotinic acid will be provided by 495 mg inositol hexanicotinate delivering, upon hydrolysis, also 108 mg inositol.

The same petitioner also states that the use of inositol hexanicotinate allows use of a nicotinic acid source which has a low-flushing effect, and which may be used at higher levels than nicotinic acid itself.

The second petitioner for inositol hexanicotinate indicates that inositol hexanicotinate is proposed to be used in food supplement at dose levels of 40 mg/day, equivalent to 36.4 mg of nicotinic acid and 8.8 mg inositol.

The Panel notes that a daily dose of 10 mg nicotinic acid, given as inositol hexanicotinate, would, upon hydrolysis, amount to a daily dose of 11 mg inositol hexanicotinate and of 2.4 mg inositol.

3. Biological and toxicological data

3.1. Bioavailability of niacin from its inositol hexanicotinate source

Nicotinamide may be obtained from the diet where it is present primarily as NAD+ and $NADP^+$. These are hydrolysed in the intestine and the resulting nicotinamide is absorbed either as such, or following its hydrolysis to nicotinic acid. Niacin in cereals is present as a glycoside of nicotinic acid. The glycoside undergoes limited hydrolysis in the gastrointestinal tract resulting in limited bioavailability of niacin from its glycoside because the compound is not bioavailable in this conjugated form (SCF, 2002). Foods that contain niacin in the free form include beans and liver. Quantitative data are not available on which to base adjustments for the bioavailability from different types of foods (FNB, 1998).

In humans, niacin is rapidly absorbed from both the stomach and the upper small intestine (SCF, 2002; EVM, 2003). At low concentrations, the absorption of nicotinic acid and nicotinamide is mediated by sodium ion-dependent facilitated diffusion. At higher concentrations, passive diffusion predominates with doses of 3 to 4 g of niacin being almost completely absorbed (FNB, 1998). The plasma half-life of nicotinic acid is relatively short, approximately one hour (EVM, 2003).

Niacin circulates in the plasma in the unbound form as both the acid and the amide. Nicotinic acid as well as nicotinamide enters peripheral tissues by passive diffusion, followed by metabolic conversion to the pyridine dinucleotides NAD(H) and NADP(H). Most of the niacin is found as NAD(H) and the oxidised form NAD^+.

The conversion of nicotinic acid to nicotinamide occurs subsequent to its formation as a pyridine nucleotide. Nicotinic acid reacts with 5-phosphoribosyl-1- pyrophosphate to form the nicotinic acid mononucleotide, which then condenses with ATP to form the nicotinic acid analogue of NAD^+, which is subsequently converted to NAD^+ by a reaction with glutamine and ATP. In contrast, nicotinamide is converted into the pyridine nucleotide simply by reaction with phosphoribosyl-1-pyrophosphate. The cofactor NAD^+ is converted to $NADP^+$ by reaction with ATP. Nicotinamide can be formed from NAD^+ via enzymatic cleavage to nicotinamide and adenosine diphosphate ribose (SCF, 2002).

The major pathway of metabolism of nicotinamide is by methylation in the liver to form N^1-methyl nicotinamide via reaction with methionine (as a methyl donor) and ATP. N-Methyl nicotinamide does not have biological activity and is a polar, water-soluble excretory product. It may be further oxidised in the 6 position of the pyridine ring to give N-methyl-6-pyridone-3-carboxamide. High doses of nicotinic acid are excreted in the urine as nicotinic acid and its glycine conjugate (nicotinuric acid) (SCF, 2002). Both nicotinic acid and nicotinamide also enter erythrocytes by facilitated transport (FNB, 1998). The main metabolites in humans are N-methylnicotinamide, N-methyl-2-pyridone-5-carboxamide, N-methyl-6-pyridone-3-carboxamide, N-methyl-4-pyridone-3-carboxamide and N-methyl-4-pyridone-5-carboxamide (Chang and Johnson, 1961; Abelson *et al.,* 1963; EVM, 2003; Eitenmiller, 2007).

Inositol hexanicotinate

Although limited data have been identified for inositol hexanicotinate, the distribution, metabolism and excretion of niacin are well established (Bechgaard and Jespersen, 1977; Figge *et al*., 1988; Stern *et al*., 1992; HSDB, 2002; SCF, 2002, EVM, 2003; Hathcock, 2004).

Gastrointestinal absorption of inositol hexanicotinate varies widely with an average of 70% of an orally ingested dose absorbed, as derived from analysis of the amount of unabsorbed hexanicotinate detected in faeces of healthy volunteers (Harthon and Lindqvist, 1964). The petitioner indicates that inositol hexanicotinate is, at least in part, absorbed intact and hydrolysed in the body releasing free nicotinic acid and inositol (Head, 1996; Harthon and Brattsand, 1979). This also occurs with other esters of nicotinic acid (Rittirod *et al.,* 1999; Salvi *et al.,* 1997). Once inositol hexanicotinate is present in human serum, hydrolysis of the ester bonds and release of free nicotinic acid is slow taking more than 48 hours, significantly longer than when inositol hexanicotinate is incubated in rat or dog serum (Harthon and Brattsand, 1979; El-Enein *et al*., 1983; Meyers *et al*., 2003; Monograph Inositol hexanicotinate, 2005). The rise in niacin levels was more than could be explained by the rate of hydrolysis of the inositol hexanicotinate ester bonds in buffered solutions of various pHs designed to simulate the gastric and intestinal juices. This hydrolysis was demonstrated to be due to an active, enzymatic hydrolysis in the bloodstream (Harthon and Brattsand, 1979). This enzymatic hydrolysis of inositol hexanicotinate in blood was examined in further detail by Harthon and Brattsand (1979). The results indicated that the plasma hydrolysis of the first ester linkage in inositol hexanicotinate proceeded more slowly than the hydrolysis of the subsequent linkages. The calculated half-life of inositol hexanicotinate may mainly reflect the rate of hydrolysis of the first ester linkage.

After oral doses of 0.8 to 4.2 g of inositol hexanicotinate in humans, plasma levels of free nicotinic acid peaked at 6-12 hours (Sommer, 1965; Welsh and Eade, 1961). In contrast, after an oral dose of 1000 mg of nicotinic acid, plasma levels of free nicotinic acid peaked at 0.5-1 hour at 30 µg/mL (Carlson *et al*., 1968).

Another paper describes a study with 0.5 g of nicotinic acid incorporated into a slowly release compressed tablet in which the nicotinic acid was incorporated into a hydroxypropylmethylcellulose matrix. At a dose of 2 g of this preparation/day, plasma levels of free nicotinic acid reached a steady state between 2.73 and 4.90 µg/mL and at a dose of 3.0 g/day plasma levels of free nicotinic acid reached a steady state between 6.17 and 7.75 µg/mL (Chojnowska-Jezierska and Adamska-Dyniewska, 1998).

3.2. Toxicological data

Few data have been identified for inositol hexanicotinate; however the safety of niacin or inositol has been evaluated in several opinions (SCF, 1999 and 2002; HSDB, 2002; EVM, 2003, Hathcock, 2004).

The present opinion only lists the studies focussing on inositol hexanicotinate, the source of niacin evaluated.

3.2.1. Animal data

El-Einein *et al.* (1983) studied the role of inositol hexanicotinate as an anticholesterolemic and antilipemic agent in rabbits. The administration of 30 mg/kg bw to either normal or

induced hypercholesterolemic Buscat rabbits for eight weeks resulted in a slight decrease in serum total lipids, triglycerides, phospholipids and cholesterol. The effect on hypercholesterolemic animals was a significant reduction of elevated serum lipid fractions and body weight. Marked decreases of serum total lipoproteins (α, β and non-mobilized fractions) were also noticed after administration of inositol hexanicotinate. The hypolipidemic effect of inositol hexanicotinate was shown to be more profound than that of nicotinic acid. No adverse effects were reported.

3.2.2. Human data

Inositol hexanicotinate has been used in a number of clinical trials at dose levels varying from 600 to 4000 mg/day.

Sunderland *et al*. (1988) looked at the use of inositol hexanicotinate for the treatment of peripheral vasospastic symptoms associated with Raynaud's disease. Hexopal was administered at the level of 4000 mg/day over a period of 84 days in 23 patients versus placebo. No adverse reactions were reported in the study.

Ziliotto *et al*. (1977) conducted a cross-over trial to compare the effects of two delayed-action nicotinic acid polyesters, pentaerythritol-tetranticotinate (PETN) and inositol-hexanicotinate (MIEN), containing the same amount of nicotinic acid in each preparation (442 mg/pill), administered three times per day (equivalent to 1.326 g of nicotinic acid/day) to 59 aged normo- and dyslipidaemic subjects. PETN tended to normalise the lipid picture in much the same way as nicotinic acid, without having a drastic effect on circulating lipids and lipoproteins. MIEN, on the other hand, had only a slight effect on total blood lipids, and appeared to be ineffective or negative with respect to the other lipid parameters. PETN proved capable of releasing active concentrations of nicotinic acid *in vivo* for a period of time that was sufficient to correct hyperlipidemia in aged subjects. The side-effects, including skin rash, itching and gastrointestinal disorders such as nausea, vomiting and diarrhea, were small, infrequent and quickly reversible (Ziliotto, 1977).

Kruse *et al*. (1979) looked at the effect of nicotinic acid and several derivatives on the nocturnal level of free fatty acids in twelve subjects, which received doses of up to 1200 mg on five different occasions with at least a three-day interval between doses. Mesoinositol hexanicotinate, dosed at levels of 600 and 1200 mg, was one of the derivatives studied and together with the xantinol ester of nicotinic acid appeared to be superior to the other preparations (Kruse *et al*., 1979). Flushing was not noted with mesoinositol hexanicotinate although it was with other derivatives.

Mesoinostol hexanicotinate (250 mg) has also been used in combination with magnesium-chlorophenoxyisobutyrate (350 mg) for the treatment of hyperlipidemia. Treatment consisted of three doses per day over 60 days. The serum levels of cholesterol and triglycerides were reduced by 16-20% and 36-49%, respectively (Fischer and Falkensammer, 1977).

Head (1996) describes a number of studies using inositol hexanicotinate for conditions such as Raynaud's disease and psoriasis with dosages ranging from 600 to 1800 mg and up to 4000 mg daily. The safety profile is acceptable in a number of conditions with little or no side effects reported (Head, 1996).

O'Hara *et al.* (1988) investigated the therapeutic efficacy of inositol hexanicotinate in intermittent claudication in a controlled trial, in which patients received, under double blind conditions, inositol hexanicotinate or matching placebo at a dosage of 4 tablets of 500 mg

each (2 g in total), twice daily for three months. It was concluded that the study provided further evidence that inositol hexanicotinate can be beneficial in the management of intermittent claudation. Adverse effects were not reported.

Although these clinical trials with dose levels up to 4000 mg inositol hexanicotinate /day were not designed to study the safety of inositol hexanicotinate, they revealed little or no side effects.

3.2.3. Carcinogenicity and genotoxicity

No genotoxicity data or long-term studies are available for either nicotinic acid (EVM, 2003) or inositol hexanicotinate.

3.2.4. Developmental and reproduction toxicity

There were no data available.

4. Discussion

The petitioner indicates that inositol hexanicotinate is, at least in part, absorbed intact and hydrolysed in the body releasing free nicotinic acid and inositol. Gastrointestinal absorption of inositol hexanicotinate varies widely, with an average of 70% of an orally ingested dose absorbed, as derived from analysis of the amount of unabsorbed hexanicotinate detected in faeces of healthy volunteers (Harthon and Lindqvist, 1964).

When inositol hexanicotinate is administered orally to humans, this results in a sustained increase in the level of free nicotinic acid in blood and plasma (Harthon and Brattsand, 1979). Once inositol hexanicotinate is present in human serum, hydrolysis of the ester bonds and release of free nicotinic acid takes more than 48 hours (Harthon and Brattsand, 1979).

Inositol hexanicotinate appears to be metabolised slowly, not reaching maximum serum levels of nicotinic acid until approximately 6-10 hours after ingestion (Sommer, 1965; Welsh and Eade, 1961), whereas upon intake of free nicotinic acid, plasma levels peak after 0.5-1 hour (Carlson *et al*., 1968).

The petitioner indicates that the intact ester of one molecule of inositol with six molecules of nicotinic acid is absorbed into the bloodstream, then slowly hydrolyzed (Meyers *et al.*, 2003; El-Enein *et al.*, 1983; Monograph Inositol hexanicotinate, 2005; Sommer, 1965) releasing free nicotinic acid without the effect of flushing (Meyers *et al.*, 2003; Monograph Inositol hexanicotinate, 2005). From the various studies reported, the Panel concludes that nicotinic acid from inositol hexanicotinate is bioavailable and a source of niacin. Niacin has been previously evaluated by the Scientific Committee on Food (SCF, 2002) and various other authorities.

The SCF has established a Tolerable Upper Intake Level for nicotinic acid of 10 mg/day, using a point of departure of 30 mg/day, at which dose level occasional flushing, the limiting adverse effect, had been reported. An uncertainty factor (UF) of 3 was applied to allow for the fact that a slight effect was reported, and that the study was performed in a small number of

subjects, but taking into account the steep dose-response relationship (SCF, 2002). The Panel noted that the UL established by the SCF did not apply to pregnant and lactating women.

Furthermore, the Expert Group on Vitamins and Minerals has established that a dose of 17 mg nicotinic acid/day, for supplementation only, would not be expected to have any significant adverse effects (EVM, 2002).

One petitioner indicates that the anticipated exposure of the population to inositol hexanicotinate in food supplements provides up to 450 mg/day of nicotinic acid. The second petitioner for inositol hexanicotinate indicates that the source is intended to be used in food supplements at levels corresponding to 40 mg inositol hexanicotinate/day, providing 36.4 mg nicotinic acid/day. The Panel notes that these levels of nicotinic acid are substantially higher than the Tolerable Upper Intake Level for nicotinic acid of 10 mg/day, set by the SCF, and also higher than the guidance value established by EVM of 17 mg nicotinic acid/day for supplementation only.

No genotoxicity data are available on inositol hexanicotinate. However inositol hexanicotinate is hydrolysed to inositol and nicotinic acid, which are endogenous compounds and occur in several dietary products. Therefore the Panel concluded that the absence of genotoxicity data does not raise concern.

Inositol hexanicotinate has been used in a number of clinical trials at dose levels varying from 600 to 4000 mg/day. No adverse effects were found when 4000 mg/day inositol hexanicotinate was administered orally to humans for three months. Although these clinical trials with dose levels of up to 4000 mg inositol hexanicotinate/day were not designed to study the safety of inositol hexanicotinate, they revealed little or no side effects.

The petitioners indicate that inositol hexanicotinate acts as a slow-release supply of nicotinic acid, as the molecule breaks down into inositol and the six nicotinic acid molecules and that therefore the flushing effect is not likely to occur when inositol hexanicotinate is used as a source of niacin.

The Panel notes that given the slow release of nicotinic acid from inositol hexanicotinate, the flushing effect, on the basis of which both the SCF and EVM have given Tolerable Upper Intake Levels for nicotinic acid, may be conservative for inositol hexanicotinate. However given the absence of studies adequately supporting the absence of a flushing effect when dosing inositol hexanicotinate, the Panel concludes that the upper limit for nicotinic acid of 10 mg/day should be used to judge the safety of inositol hexanicotinate.

The estimated dietary intake of myo-inositol ranged from 335-1500 mg/day (Clemens and Darnell, 1980). A daily dose of 10 mg niacin, given as inositol hexanicotinate, would amount to a daily dose of 11 mg inositol hexanicotinate and 2.4 mg inositol. Given the estimated normal dietary intake of inositol that amounts to 335-1500 mg myo-inositol/day (Clemens and Darnell, 1980), the Panel concludes that the intake of 2.4 mg inositol/day, resulting from intake of inositol hexanicotinate at a level that results in a daily dose of 10 mg nicotinic acid, would not be of safety concern.

However, the Panel is concerned that the use levels of inositol hexanicotinate proposed by the two petitioners are 40 and 495 mg/day providing respectively, 36.4 and 450 mg nicotinic acid/day. These proposed use levels provide levels of nicotinic acid that are 4-45 times higher than the Tolerable Upper Intake Levels of 10 mg nicotinic acid/day as defined by the SCF in 2002.

CONCLUSIONS

The present opinion deals only with the safety and bioavailability of a particular source of nicotinic acid, one of the vitamers of niacin (vitamin B_3), to be added to food supplements intended for the general population. The safety of nicotinic acid itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

The Panel concludes the following:

- Nicotinic acid from inositol hexanicotinate is bioavailable and a source of niacin

- The use of inositol hexanicotinate, as a source for niacin, when added for nutritional purposes in food supplements intended for the general population, would be of no safety concern provided that use levels are in compliance with the defined upper safe use level for nicotinic acid (10 mg/day).

However, the Panel is concerned that the use levels of inositol hexanicotinate proposed by the petitioners are 40 and 495 mg/day providing 36.4 and 450 mg nicotinic acid/day. These proposed use levels provide levels of nicotinic acid that are 4-45 times higher than the Tolerable Upper Intake level of 10 mg nicotinic acid/day, as defined by the SCF in 2002.

The Panel notes that the specifications for heavy metals should be in compliance with those established in the Commission Regulation (EC) No 629/2008. Maximum levels of lead, mercury and cadmium in food supplements as sold should be 3.0 mg/kg, 0.1 mg/kg and 1.0 mg/kg, respectively.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier on Inositol Hexaniacinate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. June, 2005. Submitted by Health Food Manufacturers Association UK.
2. Dossier on inositol hexanicotinate submitted by Natuur- & gezondheids Producten Nederland, The Netherlands.

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GLOSSARY / ABBREVIATIONS

ANS	Panel on Food Additives and Nutrient Sources added to Foods
bw	body weight
CAS	Chemical Abstracts Service
EC	European Commission
EFSA	European Food Safety Authority
EVM	Expert group on Vitamins and Minerals
FDA	U.S. Food and Drug Administration
FNB	Food and Nutrition Board
FPNU	Food for Particular Nutritional Uses
FSA	Food Standards Agency
FSMPs	Foods for particular nutritional uses, intended for special medical purposes
GRAS	Generally Recognised As Safe
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
NOAEL	No Observable Adverse Effect Level
PARNUTS	Foods for Particular Nutritional Uses
SCF	Scientific Committee on Food
UF	Uncertainty Factor
UL	Tolerable Upper Intake Level