PHYSIOTOX

Expertises toxicologiques et scientifiques

TOXICOLOGICAL RISK ASSESSMENT OF THE PRESENCE OF NICOTINIC ACID IN A FOOD SUPPLEMENT

MULTIVITAMINES

COMPANY NAME AND ADDRESS

NUTRAGROUP

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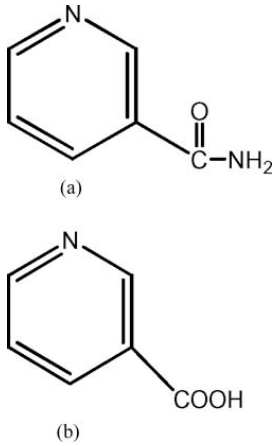
1. Nicotinic acid

Nicotinic acid (CAS No.: 59-67-6) is a soluble compound that belongs to the **B vitamin group**.

The term **niacin** comprises **nicotinic acid** and **nicotinamide** (nicotinic (acid) amide), however, **the term niacin is often used for nicotinic acid**.



Chemical structures for (a) nicotinamide and (b) nicotinic acid (From CIR, 2005)

Niacin is found in a wide range of foods. Main food groups contributing to niacin intakes of adults include meat and meat products, grains and grain-based products and milk and milk products. Depending on the foodstuff, the mean absorption of niacin is from about 23% to about 70%; it is lowest from cereals and highest from animal products.

The human body can synthesize nicotinic acid from tryptophan, an essential amino acid found in a broad range of foods of both animal and plant origin.

In vivo, **nicotinic acid** is converted into a more soluble molecule, **nicotinamide**. Nicotinamide is a precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are both essential to cells and are involved in many biochemical reactions (EFSA, 2014).

The nutritional importance of niacin (nicotinic acid and nicotinamide) is well documented. **Severe deficiency of nicotinic acid and its dietary precursor (tryptophan) is known to cause pellagra**. Pellagra is characterized by a pigmented rash that develops symmetrically in areas exposed to sunlight; changes in the digestive tract that are associated with vomiting, constipation or diarrhea, and a bright red tongue; and neurological symptoms including depression, apathy, headache, fatigue, and loss of memory. Pellagra was common in the United States and parts of Europe in the early twentieth century in areas in which corn or maize (which is low in both niacin and the amino acid tryptophan) was the dietary staple. Although a worldwide problem, pellagra has virtually disappeared from industrialized countries (Carpenter, 1983; Morris et al., 2004).

2. Hazards characterization

Acute oral toxicity

The acute oral toxicity of nicotinic acid is low with LD_{50} values which were considered > 2000 mg/kg bw in all experimental studies.

Overall, an acute toxic potential of nicotinic acid can be excluded.

Repeated oral dose toxicity

Animal data are limited, however, the available information on short-term and sub-chronic toxicity suggests that nicotinic acid is non-toxic.

A NOAEL value of 50 mg/kg bw/day was reported in a subacute (28-day) study where no mortalities and no treatment-related observations, no effects of treatment on the hematological and clinical chemistry parameters measured and no gross or histopathologic evidence of toxicity in any of the tissues examined were reported. The NOAEL is based on a slight reduction of the bodyweight gain.

CMR toxicity

Genetic toxicity

Results of the *in vitro* and *in vivo* tests with nicotinic acid were all negative, therefore, a genotoxic potential of nicotinic acid can be excluded.

Carcinogenicity

There were no reported studies of the carcinogenicity of nicotinic acid. However, no carcinogenic effect of orally administered nicotinamide was reported in a carcinogenicity study in mice.

In addition, nicotinic acid was predicted to be non-carcinogenic by the different QSAR models used.

Overall, a carcinogenic potential of nicotinic acid seems to be excluded.

Reproductive and developmental toxicity

No reproduction toxicity study has been performed with nicotinic acid, however, results of a prenatal developmental toxicity study according to OECD TG 414 indicated that the **administration of nicotinic acid induced no adverse treatment-related macroscopic changes in females. In addition, litter size and survival were unaffected by treatment, no**

morphological changes that were considered to be related to treatment with nicotinic acid, and no indications of any adverse effects upon survival or morphological development *in utero* were reported.

Based on these results, a NOAEL of 200 mg/kg bw/day was established for maternal toxicity to account for the slight reduction of the bodyweight gain, and a NOAEL of 1000 mg/kg bw/day for developmental toxicity.

Moreover, no reproductive or developmental toxic potential of nicotinic acid was predicted by the different QSAR models used, which also allow to exclude an endocrine disrupting potential.

Overall, a reproductive and developmental toxic potential of nicotinic acid seems to be excluded.

Irritation

Based on the few available experimental data, a skin irritating potential of nicotinic acid seems to be excluded and a moderate eye irritating potential can be presumed.

Sensitization

Based on the few available experimental data, and the prediction of all the QSAR models used, a sensitizing potential of nicotinic acid seems to be excluded.

Human data: nicotinic acid adverse reactions

Overall, gastrointestinal effects, glucose intolerance, and hepatotoxicity are reported in patients given high doses of nicotinic acid (above 500 mg/day, and most often 3 g/day or more) for periods of months to years and are particularly common with high doses of sustained release nicotinic acid. Thus, these adverse drug reactions cannot be expected with the use of food supplements which contain only small amount of nicotinic acid.

Therefore, flushing reactions represent the adverse drug reaction that can be detected at the lowest doses of nicotinic acid and thus, in a conservative approach, can be selected as critical effect for risk assessment.

3. Hazards characterization

3.1. ULs (tolerable Upper intake levels) used in Europe, USA, Australia, and New-Zealand

Age/life-stage		Europe SCF	Europe EGVM	USA	Australia New-Zealand
Infants	0-12 months	Not possible to establish			
Children and adolescents	1-3 years	2 mg/day		10 mg/day	10 mg/day
	4-8 years	3 mg/day (4-6)		15 mg/day	15 mg/day
	9-13 years	4 mg/day (7-10)		20 mg/day	20 mg/day
	14-18 years	6 mg/day (11-14) 8 mg/day (15-17)		30 mg/day	30 mg/day
Adults	19+ years	10 mg/day	17 mg/day (Guidance level)	35 mg/day	35 mg/day
Pregnancy	14-18 years	Inadequate data		30 mg/day	30 mg/day
	19-50 years			35 mg/day	35 mg/day
Lactation	14-18 years			30 mg/day	30 mg/day
	19-50 years			35 mg/day	35 mg/day

Table 4. Summary of ULs used in Europe, USA, Australia, and New-Zealand

3.2. OECD

Another maximum acceptable daily dose has been established by the OECD which concluded that:

"***Nicotinic acid is actually not toxic, but moderately irritant to the eye.***

Rare cases of skin flushing may occur, but this effect is reversible after termination of exposure.

The NOAEL in a 28-day oral study in rats was 50 mg/kg bw/day. However, only a minimal effect on body weight gain without any organ toxicity was found up to the high dose of 1000 mg/kg bw/day.

For an initial assessment the ***estimated dose of low concern (EDLC)*** *can be calculated as follows:*

EDLC = NOAEL/UF = 50/100 = 0.5 mg/kg bw/day

The uncertainty factor (UF) of 100 is based on intraspecies variation (factor of 10) and interspecies variation (factor of 10). As the only effect seen at higher dose levels (250 and 1000 mg/kg bw/day) was a slight reduction of the body weight gain a UF of 100 is considered to be sufficient" (OECD, 1993).

3.3. Maximum acceptable daily dose

Based on the experimental data summarized in this report:

- **An acute oral toxic potential of nicotinic acid can be excluded.**
- **No chronic oral toxicity of nicotinic acid can be expected at doses < 50 mg/day.**
- **A genotoxic potential of nicotinic acid can be excluded.**
- **A carcinogenic potential of nicotinic acid seems to be excluded.**
- **A reproductive and developmental toxic potential of nicotinic acid seems to be excluded.**
- **A skin irritating potential of nicotinic acid seems to be excluded, and only a moderate eye irritating potential can be excepted.**
- **A sensitizing potential of nicotinic acid seems to be excluded.**

Therefore, although it is not "clearly" a toxic effect, using flushing reactions as the adverse effect to derive upper intake limits for nicotinic acid can be considered as a conservative approach for risk assessment.

Only Sebrell et al study reported flushing reactions at oral dose < 50 mg/day (i.e., 30 mg/day, in 2 subjects) (Sebrell et al., 1938).
However **Sebrell et al study can be considered of poor methodological quality:**

- **Limited number of subjects (n = 6/dose groups).**
- **Only women.**
- **No information on the age of the subjects (menopause?).**
- **Weight of the subjects varies from 45 to 75 kg, no information on the body mass index.**
- **Administered doses of nicotinic acid were not standardized according to the subject's body weight. It has been demonstrated that flushing is associated with rapid rises in nicotinic acid blood concentration.**
- **No information on prior histories of liver disease or hypersensitivity to nicotinic acid.**
- **Niacin status of the subjects at the beginning of the study was not measured.**

Despite the poor methodological quality of the Sebrell et al study, since other authors have also reported flushing reaction at doses ≥ 50 mg nicotinic acid/day, this dose can be considered as a LOAEL for risk assessment.

Overall, the UL of 35 mg nicotinic acid/day for an adult of 70 kg derived by the IOM can be used for risk assessment, i.e., 0.5 mg nicotinic acid/kg bw/day.

Based on a different point of departure (experimental animal data), the OECD has derived a safe level of the same value, i.e., an estimated dose of low concern (EDLC) of 0.5 mg nicotinic acid/kg bw/day, which confirm the reliability of this upper limit.

Based on the EFSA guidance on default values to be used in the absence of measured data (EFSA, 2012), the following limits can be set for risk assessment on a body weight basis:

Toddlers (aged 1-3 years): 0.5 x 12 = 6 mg/day, based on a default body weight of 12 kg.

Other children [3-10 years[: 0.5 x 23.1 = 12 mg/day, based on a mean body weight of 23.1 kg.

Adolescents [10-14 years[: 0.5 x 43.4 = 22 mg/day, based on a mean body weight of 43.4 kg.

Adolescents [14-18 years[: 0.5 x 61.3 = 31 mg/day, based on a mean body weight of 61.3 kg.

4. Exposure data

4.1. Exposure to the food supplement: MULTIVITAMINES

The following information are available on the food supplement packaging (See. Appendix 4.1):

Usage tips: take 2 capsules/day.

A capsule contains 9 mg nicotinic acid (See. Appendix 4.1), however, according to the technical datasheet, the capsules are manufactured with an overdose of vitamin B3 (11.03 mg nicotinic acid (See. Appendix 4.2)) in order to maintain a dose of vitamin D3 in accordance with the labeling until the expiry of the product.

Therefore, for the risk assessment we will consider an **exposure** of:

- **2 capsules/day, i.e., 18 mg nicotinic acid/day**
- **2 capsules/day, i.e., 22 mg nicotinic acid/day**

4.2. Dietary exposure to nicotinic acid

According to the IOM (IOM, 1998), SCF (SCF, 2002), EGVM (EGVM, 2003) and NHMRC (NHMRC, 2017) assessment reports:

The only reports of flushing associated with the ingestion of nicotinic acid with food have occurred following the addition of free nicotinic acid to food prior to consumption.

Indeed, free nicotinic acid levels in food are low.

Therefore, the upper limits were derived for supplements only, as flushing reactions are related to acute, bolus intakes of nicotinic acid, rather than more sustained exposure as would occur with ingestion of nicotinic acid via food.

Overall, since the low free nicotinic acid levels in food don't induce flushing reactions, the upper limits of nicotinic acid derived for supplements only can be used for risk assessment.

5. Risk assessment

Instructions of use (See. Appendix 4.1) **don't mentioned that the use of the food supplement is reserved for adults. However, the use of the food supplement is not recommended for children, and pregnant and breastfeeding women are advised to seek the advice of a health professional before any supplementation. Therefore, adolescents and adults will be included in the risk analysis.**

Thus, for risk assessment, based on the EFSA guidance on default values to be used in the absence of measured data (EFSA, 2012), we will used the following bodyweights:

- An **adult body weight** of **70 kg** (European adult (above 18 years old))
- An **adolescent [10-14 years[** mean body weight of **43.4 kg**
- An **adolescent [14-18 years[** mean body weight of **61.3 kg**

Based on the toxicological reference value: 0.5 mg nicotinic acid/kg bw/day (See. Section 5.4), **the maximum acceptable daily intake will be:**

- **Adult: 0.5 mg/kg bw/day x 70 kg = 35 mg nicotinic acid/day.**
- **Adolescent [10-14 years[: 0.5 mg/kg bw/day x 43.4 kg = 22 mg/day**
- **Adolescent [14-18 years[: 0.5 mg/kg bw/day x 61.3 kg = 31 mg/day**

With an exposure of 2 capsules of food supplement/day, the nicotinic acid intake will be 18 or 22 mg nicotinic acid/day.

Therefore, the distance to the maximum acceptable daily intake (toxicological reference value) is:

- **35/18 = 2 (1.95) for 2 capsules/day for adult.**
- **22/18 = 1.2 (1.22) for 2 capsules/day for adolescent [10-14 years[**
- **31/18 = 1.7 (1.72) for 2 capsules/day for adolescent [14-18 years[**

- **35/22 = 1.5 (1.59) for 2 capsules/day for adult.**
- **22/22 = 1 (1) for 2 capsules/day for adolescent [10-14 years[**
- **31/22 = 1.4 (1.41) for 2 capsules/day for adolescent [14-18 years[**

Overall, whatever the scenario of exposure, nicotinic acid daily dose for 2 capsules/day of the food supplement is lower than or equal to the maximum acceptable daily intake.

6. Conclusion

Overall, even in a worse-case approach by considering the overdosage at the manufacture of the product, and whatever the scenario of exposure, nicotinic acid daily dose for 2 capsules/day of the food supplement is lower than or equal to the maximum acceptable daily intake, this amount of nicotinic acid is not likely to harm health during the use of MULTIVITAMINES according to the instructions of use.

7. References of the assessor

Dr. Eric BLOUIN, Expert toxicologist of PHYSIOTOX, PhD in Cellular and Molecular Physiopathology, Master TES (Toxicology Ecotoxicology and Health), IUD FIEC (Training of Investigators in Clinical Trials of Drugs), Member of the French Society of Toxicology and of the Francophone Society for Study and Research on Toxic and Essential Elements, GREMI Thesis Award (Research and Study Group on Inflammation Mediators).

Dr. Eric BLOUIN

June 9, 2023

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8. Appendix 4.1. MULTIVITAMINES packaging

9. Appendix 4.2. MULTIVITAMINES technical data sheet

NUTRIPURE MULTIVITAMINES, Piluliers 125 mL Blanc, cape Blanc PELD Clip D43 avec dessicant, contenant 60 Gélules, Pullulan T00			
Code Produit Nutragroup / B-Pharma :	PF2012052	Code Produit Client :	NC

Fiche technique Produit Fini			
Version de la formule	Date	Validation	Signature
2	2022-02-16	Céline Perret	
Motif de modification :	Corrections codes vitamine B3 et B12, changement du sélénite par du sélénate et changement de bouchon		

Données produit	
Type d'unités	Gélules
Type de gélule (si applicable)	Pullulan
Taille de la gélule / capsule	T00
Couleur de la gélule / capsule	Transparente
Code article gélule	GEL2011061
Poids poudre / unité (en mg)	688
Poids d'une gélule vide ou d'un sachet vide (en mg)	145
Poids d'une gélule ou d'un sachet rempli (en mg)	833

Conditionnement	
Type de conditionnement	Piluliers en vrac

Piluliers			
Taille du pilulier	125	Code article Pilulier	PIL2012050
Couleur du pilulier	Blanc		
Couleur du bouchon	Blanc PELD Clip D43 avec dessicant	Code article Bouchon	BOU2202121
Nombre d'unités / pilulier	60		

Articles de conditionnement			
Etiquette (si applicable)	Avec	Code article étiquette	ETI2012052

Autres spécificités** :	Etiquette fournie par le client
Codage :	Emplacement du codage : Lot - DDM - Sous le pilulier . Encre de couleur Noir
BIO / Conventionnel :	CONVENTIONNEL

Allergènes						
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA

Formule (sous réserve de test industriel)				
Ingredients	Code MP	Taux dans la formule en %	mg / unité	Quantité d'actif par unité
Bisglycinate de magnésium chélaté 20% poudre / Magnesium Bisglycinate Chelated 20% powder	1909161	45,41%	312,5	
Acide Ascorbique Vit C / Ascorbic acid Vit C	1302203	19,12%	131,56	
Acide alpha lipoique poudre USP / Alpha lipoic acid powder USP	1506160	7,27%	50	
Lutéine poudre 20% HPLC / Lutein powder 20% HPLC / Tagetes erecta L.	2012140	4,90%	33,75	
Farine de coco BIO* / ORGANIC* Coconut flour / Cocos nucifera	2010230	4,36%	30	
Sophora japonica Sommités fleuries ES 98% Quercetine / Sophora japonica Top flowers PE 98% Quercetin / Sophorae japonica	1303181	3,63%	25	
Zinc citrate Trihydrate Poudre USP (31%Zn) / Zinc citrate Trihydrate powder USP (31% Zn)	1808072	3,48%	23,97	
Nutrabiol E™ PVM 500	2012091	3,13%	21,56	

Coenzyme Q10 Poudre / Coenzyme Q10 Powder	2011192	2,33%	16	
Vitamine B3 / Vitamine PP / Nicotinamide	1306042	1,60%	11,03	
Nutrabiol T30™ PVM	2012090	1,45%	10	
Bétacarotène ES Beadlets 10% NLT / Betacaroten PE Beadlets 10% NLT	1201223	0,87%	6	
Vitamine D3 Poudre 100 000 IU-G CWS / Vitamin D3 Powder 100 000 IU-G CWS	2012280	0,73%	5	
Vitamine B5 100% / Calcium Panthotenate	1412128	0,58%	4,02	
Vitamine B12 Methylcobalamine poudre 0.1% HPLC support maltodextrine/ Vitamin B12 Methylcobalamin pure powder 0.1% HPLC maltodextrin carrier	2101060	0,44%	3	
Vitamine B1 HCl thiamine Poudre 100% / Vitamine B1 HCl thiamin Powder 100%	1412127	0,24%	1,6577	
Vitamine B6 HCl Poudre 100%/ Vitamin B6 HCl Powder 100%/ Pyridoxine Hydrochloride	1306041	0,22%	1,4914	
Vitamine B2, Riboflavine poudre 100% - Origine fermentation / Vitamin B2, Riboflavin powder 100% - fermentation origin	1410020	0,16%	1,12	
Quatrefolic™ Vit B9 Acide (6S)-5-Méthyltétrahydrofolique sous forme de sel de glucosamine/ (6S)-5-Methyltetrahydrofolic acid, Glucosamine Salt	2002180	0,03%	0,222	
Chrome picolinate 12%	1505210	0,02%	0,1034	

Vitamine B8 Biotine / Biotin / Vitamine H	**1412124**	0,01%	0,0928	
Iodure de potassium EP Poudre / Potassium Iodide EP Powder	**1412134**	0,01%	0,0491	
Sélénate de sodium anhydre/ Sodium selenate Anhydrous	**2201261**	0,01%	0,03964	
TOTAL		100%	688,16604	

Propriétés	Specifications
Microbiologiques *	
Flore totale	≤ 10 000 UFC/g **
Levures et moisissures	≤ 100 UFC/g **
Enterobacteries	≤ 100 UFC/g
E.coli	Absence (1g)
Salmonella spp	Absence (25g)
Contaminants *	
Cadmium	≤ 1 ppm
Plomb	≤ 3 ppm
Mercure	≤ 0.1 ppm
Arsenic	≤ 1 ppm
Analyses (spécificités client)	
Libératoire sur produit fini : Microbiologique	Catégorie B
Date de durabilité minimale en mois préconisée par B-Pharma (DDM, en mois)	24 mois
Date de durabilité minimale en mois validée par le client	24
Conditions de stockage	À stocker à l'abri de la lumière, de la chaleur et de l'humidité.

**Selon plan de contrôle*

*** Nombre maximal acceptable : 5 fois le critère d'acceptation selon Eur. Ph. VIII ° Ed 5.1.8 Catégorie B*

<>

*** En cas de fourniture des articles de conditionnement (ADC) par le client, celui-ci doit s'assurer de leur alimentarité ou de leur aptitude au contact alimentaire*

Merci de bien indiquer la DDM que vous souhaitez pour votre produit dans la rubrique correspondante

Mentions obligatoires d'étiquetage
Directive 2002/46/EC hors mention spécifique liée à la composition
FR : Les compléments alimentaires doivent être utilisés dans le cadre d'un mode de vie sain et ne pas être utilisés comme susbtituts d'un régime alimentaire varié et equilibré. Garder le produit hors de la portée des jeunes enfants. Ne pas dépasser la dose journalière recommandée.

Validation par le client	
Date :	16/02/2022
Nom :	Pauline DELIGNE
Visa et Cachet de la société :	NUTRIPURE SARL 37 ch. du coteau de fontbazi 31450 DONNEVILLE - FR Siret : 83337221200013 * Sans réponse de votre part dans un délai de 8 jours, nous considérons votre accord (à compter de la date d'envoi de la fiche technique)

10. Appendix 5. Assessor Curriculum Vitae

Dr. Eric BLOUIN, Expert toxicologist

Member of the SFT (French Society of Toxicology) and of the SFERETE (Francophone Society for Study and Research on Toxic and Essential Elements)

GREMI Thesis Award (Research and Study Group on Inflammation Mediators)

Qualifications

- Research Doctorate, PhD in Cellular and Molecular Physiopathology
- Master TES (Toxicology Ecotoxicology and Health)
- IUD FIEC (Training of Investigators in Clinical Trials of Drugs)
- Master of Cellular and Molecular Physiopathology

Professional Experiences

- Expert toxicologist at PHYSIOTOX (Since 2017)
- Product Safety Manager at LABCATAL SA (2015 - 2017)
- Scientific Manager at LABCATAL SA (2003 - 2015)
- Clinical Research Assistant at FOVEA GROUP (2001 - 2003)
- Research Fellow at NECKER HOSPITAL (1996 - 2001)

Professional skills

- Toxicological profiles of active pharmaceutical ingredient, excipient, raw materials, active ingredients…
- Toxicological risk assessment/analysis
- Determination of Permitted Daily Exposure (PDE) according to the EMA guideline
- Preparation of the non-clinical parts of the Common Technical Document (CTD Modules 2.4 and 4)
- Safety assessment of cosmetic and food supplement
- Development of non-clinical studies: protocols, compliance of study reports, management of the project team…

Contact informations

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