RISK PROFILE

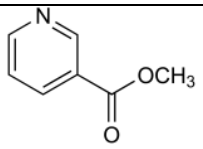
Methyl nicotinate(MN)

CAS No. 93-60-7

Date of reporting 17.03.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	3-pyridinecarboxylic acid methyl ester
INCI	Methyl nicotinate
Synonyms	Methyl 3-pyridinecarboxylate, methylpyridine-3-carboxylate, nicotinic acid methyl ester, Methyl Nicotinate (MN) is the ester of methanol and nicotinic acid (NA).
CAS No.	93-60-7
EINECS No.	202-261-8
Molecular formula	
Chemical structure	$C_7H_7NO_2$
Molecular weight	137.14 g/mol
Contents (if relevant)	
Physiochemical properties	Appearance: white solid powder Density: 1.0048 g/cm^3 Boiling point: 204 °C Melting point: 43 °C Flash point: 95.56 °C Vapor pressure: 3 mmHg (at 25 °C) Solubility: soluble in water

	Log P(o/w) 0.8 (more soluble in water than organic solvents) References: WolframAlpha [online]; Degim et al., 1998.

2. Uses and origin

Uses	➢ **Cosmetic products:** ***Functions according to*** • CosIng database: "*Soothing*" – "Helps lightening discomfort of the skin or of the scalp" "*Tonic*" – "Produces a feeling of well-being on skin and hair" • Other: *Skin-Conditioning Agent(s)* – enhancing the appearance of dry or damaged skin by reducing flaking and restoring suppleness. *Rubefacient / lip plumping* - to produce a redness or inflammation for a short period of time, often in lip products[1]. ***Concentrations being applied*** MN is used at concentrations of 0.25-1.0% to produce its counter-irritant and rubefacient effects (Blenkinsopp et al., 2005). An internet search revealed products containing MN in the range 0.5-1.6% (Annex 2). Niacin (a collective term for nicotinamide and nicotinic acid) [2] concentrations range from 0.01% in body and hand creams, lotion, powders and sprays, to 0.1% in paste masks (mud packs). (Natural Standard [online]; Integrative Practitioner [online]). Nicotinamide (NA) – i.e. vitamin B3 - concentration varies from 0.0001% in night preparations to 3% in body and hand creams, lotions, powder and sprays. ***Frequency of use of MN*** The EWG Skin Deep [online] database lists 14 cosmetic products: • lip plumper (5 products) • conditioner (2 products) • lubricant/ spermicide (2 products) • body firming lotion (2 products) • tanning oil (1 products) • moisturizer (1 products)

[1] Vasodilation (dilation of blood vessels), erythema (redness) and an increase in skin temperature (gives a warming sensation) is a side effect that makes the skin redden, hence the name).

References: (Caselli et al., 2003; Riviere et al., 2001; Wikipedia [online]).

[2] The ester hydrolysis products of MN in human plasma are nicotinic acid (NA) and methanol – cf. Section 4, "Metabolism". Nicotinamide and NA (collectively also known as niacin or vitamin B3) are also used in cosmetics, as well as in hair and skin conditioning agents.

	GoodGuide [online] provide a similar list with additional products: • Lip Plumper (14) • Sunless Tanning (7) • Lipstick (6) • Tanning Oil (3) • Lip Gloss (3) • Mask (1) • Foot Cleansing (1) • Hair Loss Treatment (1) • Nail Care (General) (1) • Shaving Cream (1) • Lubricant/Spermicide (1) Codecheck [online] revealed that MN was present as an ingredient in 25 cosmetic products, mainly body lotions/creams, but also in bathing salt and a hair styling product ➢ **Food** MN is used in food as a flavouring agent, see below "other products". Niacin is found in protein-containing foods (e.g. meat, fish, poultry), except milk and eggs (Council of Europe, 2008). Dietary tryptophan (e.g. derived from milk and egg protein) is also converted to niacin in the body and compensates for any deficiency in niacin. National public recommendation[3] for daily intake of niacin in Norway is 18 mg (men) and 15 mg (women) (Norwegian health directorate / see also Nettdoktor [online]). Vitamin dietary supplements containing niacin are mainly in the form of single nutrient (0.25 -150 mg/day) or multi-nutrient (up to 250 mg/day). Nicotinamide (vitamin B3) products are used to treat specific metabolic disorders, muscle cramps and hyperlipidemias) and alleviates pellagra, the disease caused by the lack of this vitamin. (Council of Europe, 2008). ➢ **Medicinal products** MN is used as a rubefacient for the relief of aches and pains in muscles, tendons, and joints (e.g. arthritis pain) (Koivukangas et al. (2000), Wilkin et al. (1985), cited in Muralidhara Rao et al., 2007; EMEA, 1998; Council of Europe, 2008). MN enhances peripheral vasodilation[4] by acting directly on arteriolar smooth fiber. The presence of a methyl group promotes skin penetration and local vascular action. Veterinary medicine: The concentration of MN in the formulated veterinary product is 2%, e.g. used as topical application for the treatment of respiratory diseases, vascular disorders and rheumatoid

[3] Webpage last updated July, 2000.

[4] MN is categorized as a vasodilator. When applied three or four times a day in concentrations of 0.25 – 1 percent, it is marketed as a safe and effective counterirritant. When MN is applied over large body surface areas, generalized vasodilation can occur, and some individuals have experienced large reductions in blood pressure and syncope (fainting) as a result (zostrix [online]).

	disorders in cattle and horse. ➢ **Other products** *Flavoring agent*: MN used as a flavoring agent is without any concerns at current levels of intake, as evaluated by JECFA (JECFA, 2004; Council of Europe, 2008; Annex 1B).[5] MN is an active flavor compound in fruits like Strawberries, Papaya, and various Orchidaceae species (Muralidhara Rao et al., 2007). MN is also used as a flavoring agent in cigarettes (Council of Europe, 2008). *Topical muscle builder supplements:* MN is marketed as a topical muscle builder on the internet[6].
Origin Natural (exo /endo) Synthetic	MN is an ester that is derived from nicotinic acid (NA). Niacin – a water-soluble B vitamin –vitamin B3 - is the term used to describe two related compounds, NA and nicotinamide (CIR, 2005). Niacin is not strictly a vitamin because it is formed from the metabolism of tryptophan (SCF, 2002). Niacin is the precursor of coenzymes NAD and NADP, which are essential for the functioning of a wide range of enzymes involved in redox reactions (energy metabolism), hormone production, and DNA repair (Natural Standard [online]).

3. Regulation

Norway	No regulation[7]
EU	No regulation
Rest of the world	No regulation[8]

4. Relevant toxicity studies

Absorption Skin	Skin absorption of MN is rapid (Biam2.org [online]; Issachar et al., 1998; Muller et al., 2003). In vitro, 80 - 90% of the polar compounds MN and ethyl nicotinate rapidly penetrated the skin (Guy et al., 1986). The less polar compounds, hexyl and benzyl nicotinate, penetrated skin very slowly. NA showed very little penetration even after 50 hours. These data indicate that an effective skin penetrant requires both lipophilic and hydrophilic properties. The presence of a methyl group in MN promotes

[5] In the 63rd meeting of the Joint FAO/WHO experts committee on food additives (JECFA) in 2004, MN has been accepted as a flavoring agent and there was no safety concern for intake as a flavoring agent (JECFA, 2004). MN (appears on the list as 3-pyridinecarboxylic acid, methyl ester) was reported as used in fragrance compounds by The International Fragrance Association (IFRA) in 2008 (IFRA, 2010).

[6] An article in Muscle & Fitness (2007) has a presentation of MN as a topical "muscle builder": http://mf.weideronline.eu/en/nutrition/441-ah-theres-the-rub

[7] The Norwegian medicinal products agency considered MN a medicinal remedy. Because of that up till 2008 topical products containing the substance were considered medicines – meaning a topical product containing it were automatically classified a medicine. This regime has since been lifted

[8] MN (3-Pyridinecarboxylic acid, methyl ester) is listed on the TSCA (Toxic Substances Control Act) inventory. http://explore.data.gov/Geography-and-Environment/TSCA-Inventory/pkhi-wvjh

	skin penetration. In excised skin of hairless mice, MN and ethyl nicotinate can effectively bypass the stratum corneum barrier, whereas NA cannot. Skin transport is the rate limiting step in the skin absorption of these compounds. In human skin (*in vivo*), the respective ^{14}C labelled nicotinate derivatives were applied at a dose of 4 µg/cm^2 to the forearm of volunteers. The extent of absorption was determined by collecting urine samples at various times over the next 5 days and analysing them for ^{14}C activity. In human skin the nicotinates apparently have a higher affinity for the stratum corneum than for viable tissue (showing dependence on the partition coefficient, K_{ow}). MN has also been shown to promote rapid delivery of other ingredients by absorption through the skin (Herberex [online]). *For references and additional information on skin penetration, cf. monograph of methyl nicotinate – section 2.3 (Council of Europe, 2008)*.
GI tractus	In humans, niacin (NA and nicotinamide) is rapidly absorbed from the stomach and intestine by a sodium carrier-mediated mechanism at low concentrations (EVM, 2003; Felleskatalogen [online]).
Distribution	Animal studies have shown that NA rapidly disappears from the blood and is mainly concentrated in the liver, but also located in adipose tissue and the kidneys (EVM, 2003;Toxnet [online]).
Metabolism	MN is rapidly hydrolysed by carboxyesterase to yield nicotinic acid (NA) and methanol (JECFA, 2004; Council of Europe, 2008). Data are scarce on the pharmacodynamics of MN, but it has been assumed that the close similarities between MN, NA and nicotinamide with regard to structural and pharmacological properties also could indicate similar metabolism (EMA, 1998).The plasma half-life of NA is relatively short, approximately one hour (EVM, 2003). However, more detailed information awaits further experimental data. *See also monograph of methyl nicotinate (Council of Europe, 2008)*.
Excretion	Information on the pharmacokinetics of MN is scarce. Approx. 15% of the activity contained in a small radiolabelled dose (few micrograms) administered epicutaneously to human volunteers was recovered from urine within 108 hours after treatment (Council of Europe, 2008). Niacin and its metabolites are assumed to follow the same metabolic pathways, with excretion taking place mainly (approx. 60-88%) via the kidney (Toxnet [online], EMEA, 1998). *See also monograph of methyl nicotinate (Council of Europe, 2008)*.
Local toxic effects Irritation Sensitivity	*Local toxic effects, including sensitization, are addressed in the "monograph of methyl nicotinate" - section 2.2 (Council of Europe, 2008)*. Local toxic effects such as skin irritation, erythema and/or swelling (oedema) has been reported in response to MN at concentrations as low as 0.00137 -0.003% in hyperreactive patients and dermatitis patients. Data on potential sensitization reactions to MN are scarce (discussed in

	the *monograph of methyl nicotinate (Council of Europe, 2008*, pp. 245).
Systemic toxic effects	*Systemic toxic effects of MN are mainly summarized in "monograph of methyl nicotinate" - section 2.4 (Council of Europe, 2008).* *See also "Final Report of the Safety Assessment of Niacinamide and Niacin", reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel (CIR, 2005).*
Acute	For MN, a LD_{50} of 2800 mg/ kg bw was reported (Pellmont, 1977, cited in Annex 1C). The acute subcutaneous LD_{50} of nicotinamide and NA in rats were 1.8 and 5.0 g/kg bw, respectively (EMEA, 1998).[9] A case-report suggested adverse effects of *local application* of 2-3 g of an ointment containing 1% MN and 0.12% capsaicin. The treatment to the back produced a burning sensation in the abdomen and a feeling of faintness in a girl. Skin testing revealed hypersensitivity to the ointment. The patient recovered without specific treatment. A month later the patient fainted within 5 minutes of applying 5 g of the ointment to the knee to relieve muscle pain ((Ferguson, 1988; "*monograph of methyl nicotinate", Council of Europe, 2008*)).
Repeated dose (short term)	There was no short-term toxicity in response to MN at a dose of 0.6 mg/kg bw /day, given in a niacin (NA) deficient diet in rats for 11-25 days (Council of Europe, 2008, pp. 246).
Repeated dose (long term)	No data are available for chronic toxicity of MN in humans. No adverse effects were reported for nicotinamide in clinical studies, whereas high doses of NA (3000 mg/day) are associated with considerable toxicity. In one third to one half of the 1119 patients taking 3000 mg NA /day for at least five years (to reduce the incidence of a second myocardial infarction), side effects included gastrointestinal and urinary tract problems, as well as dermatological problems of flushing, itching and rash ("The Coronary Drug Project", 1975, cited in "*monograph of methyl nicotinate", Council of Europe, 2008, pp. 248).*
Mutagenicity /genotoxicity Carcinogenicity	No carcinogenicity, genotoxicity or adequate reproductive toxicity studies have been found for MN. Long-term studies of *nicotinamide* in mice exposed to oral doses of 2 to 3 mg nicotinamide /kg bw/day gave no indication of carcinogenic potential (Council of Europe, 2008; EMEA, 1998).
Reprotoxicity / Teratogenicy	Injection of MN into chicken eggs did not produce visible abnormalities of the neck, beak or leg muscles, but rather reduced the effect of a compound known to induce malformations (Roger et al., 1969, cited in "*monograph of methyl nicotinate", Council of Europe, 2008*). In rats, nicotinamide was reported to cause growth retardation, but the relevance to MN is not known (EVM, 2003; Council of Europe, 2008). We are also not aware of reports on reproduction toxicity /teratogenicity of MN in other species.
Other effects	Intraperitoneal injection affected liver enzyme activity in mice (abstract, Bibra [online]).

[9] Only data on nicotinamide and NA were available for review.

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	There is no effect level (NOEL) available for MN[10], cf. "*monograph of methyl nicotinate", Council of Europe, 2008*. The Scientific Committee on Food established an upper safe level (UL) for NA of 10 mg/day, based on occasional flushing as the limiting adverse effect (SCF, 2002). This is equivalent to 0.167 mg /kg bw/day (for a 60 kg person), which was used as the NOEL in the calculations of MoS below.
Exposure cosmetic products	MN is used at concentrations of 0.25-1.0% to produce its counter-irritant and rubefacient effects (Blenkinsopp et al., 2005). An internet search revealed products containing MN in the range 0.5-1.6% (Annex 2). Systemic exposure dose (SED) was estimated for different cosmetic product types according to *Colipa data* (SCCS, 2010), using 1% MN as an illustrative example: • **Body lotion** 1% MN (cream, body lotion) Calculated relative daily exposure of product: 123.20 mg/kg bw/day Concentration of ingredient in the product: 1% = 0.01 Dermal absorption (SCCS default value): 100% = 1 SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100 = 123.20 mg/kg bw/day x 0.01 x 1 = **1.232 mg/kg bw/day** This corresponds to penetration of approximately 75 mg/day and 90 mg/day for women (60 kg) and men (74 kg), respectively. • **Hair styling products** 1% MN (cream, body lotion) Calculated relative daily exposure of product: 5.74 mg/kg bw/day SED = 5.74 mg/kg bw/day x 0.01 x 1 = **0.0574 mg/kg bw/day** • **Lipstick, lip salve** 1% MN (salve, lip stick) Calculated relative daily exposure of product: 0.90 mg/kg bw/day SED = 0.90 x 0.01 x 1 = 0.009 mg/kg bw/day = **9 µg/kg bw/day** Overall SED: 1.232 + 0.0574 + 0.009 = 1.3 mg/kg bw/day A worst case scenario of maximum dermal uptake of 3.1 µg/cm^2 /hour (for human skin after application of a 1% MN solution) was used to calculate internal systemic exposure to MN from a body lotion, corresponding 1166 mg/day (Council of Europe, 2008). It was noted that this calculation probably is an overestimation, but that the rapid

[10] The safety of NA has been evaluated by various authorities, including the SCF and the EVM. The SCF established a UL for NA of 10 mg/day, based on occasional flushing as the limiting adverse effect, which corresponds to 0.167 mg/kg bw/day for a 60 kg person. The EVM has not established an UL for NA due to insufficient data. For guidance purposes (for supplementation only), a dose of 17 mg/day was expected not to have any significant adverse effects, equivalent to 0.28 mg /kg bw/day (60 kg female). The EFSA Journal (2008) 887, 1-24.

	penetration of MN had to be considered.
Margin of Safety (MoS)	*Because NOEL values are missing it is not possible to calculate a margin of safety for MN.* A tentative NOEL for NA was extrapolated from an UL of 10 mg nicotinate/day, based on occasional flushing as the limiting adverse effect (SCF, 2002). For a 60 kg person this is equivalent to: *NOEL = 0.167 mg nicotinic acid/kg bw/day (extrapolated from UL)* **MoS for body lotion:** SED = 1.232 mg/kg bw/day MoS = (NOEL/SED) = 0.167 /1.232 = 0.14 **MoS for hair styling products:** SED = 0.0574 mg/kg bw/day MoS = 0.167 /0.0574 = 2.91 **MoS for lip salve /lipstick:** SED = 0.009 mg/kg bw/day MoS = 0.167 /0.009 = 18.6 MoS (overall exposure from cosmetics): SED = 1.298 mg/kg bw/day MoS = 0.167/ 1.3 = 0.13

6. **Other sources of exposure than cosmetic products**

Food and supplements	MN added to food as a flavoring substance is estimated to be 0.6 µg/capita/day in Europe (Annex 1B), which is well below the threshold of concern for a flavoring agent in structural class II (i.e. 540 µg/person/day for class II).[11] No safety concern is present at current levels of intake when MN is used as a flavouring agent (JECFA, 2004; MN monograph, Council of Europe, 2008). MN is on the EAFUS[12] list. For niacin, the dietary reference intake (DRI) established by the Food and Nutrition Board is 14 - 18 mg/ day, with maximum intake of 35 mg daily (DRI [online]). Niacin supplements are mainly in the form of nicotinamide. MN is also naturally present at low levels in some foods e.g. at 0.63-12 µg/g in rice (Muralidhara Rao et al., 2007).
Pharmaceuticals	MN is present at concentrations of 0.25% (pain relieving rub cream), 0.5% (external analgesic), and up to 1% (topical vasodilator).[13],[14]

[11] The thresholds for human intake for structural classes I, II, and III are 1800, 540 and 90 µg/person per day, respectively.

[12] EAFUS [Everything Added to Food]: A Food Additive Database. 2008. The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS (generally recognized as safe"). http://www.fda.gov/food/foodingredientspackaging/ucm115326.htm

[13] References:
http://www.prescriptiondrug-info.com/Drugs/ArthriCare-Arthritis-Pain-Relieving-Rub/
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=40402#nlm34071-1

	In clinical trials, niacin (nicotinamide and/or NA) dosing varies according to the condition it is being used to treat: 500 mg (macular degeneration) up to 3 g (osteoarthritis) and 6 g (cardiovascular disease).
Other sources	
Adverse side effects - from uses other than cosmetics	There is presently no side effect information available for MN itself.[15] A few patients who applied a medicated topical preparation containing MN (and other components) suffered adverse reactions including faintness, nausea, pain and skin rashes[16]. Common unwanted side effects of orally administered NA are flushing and gastrointestinal symptoms, such as nausea and diarrhea (Babcock et al., 2011; Gille et al., 2008; *"monograph of methyl nicotinate", Council of Europe, 2008*). There have been occasional reports of systemic adverse effects following absorption of nicotinates e.g. dizziness or feelings of faintness, which are due to a drop in blood pressure following vasodilatation (Blenkinsopp, 2008). Other less common unwanted effects include a decrease in glucose tolerance or an increase in plasma uric acid levels, of relevance in patients with diabetes or hyperuricemia. (Gille et al., 2008). See also Legemiddelhåndboka [online] (Norwegian) for NA. A dose of 50-100 mg of NA is sufficient to elicit flushing of the face and upper body, whereas higher doses (500-1000 mg) may lead to a much stronger vasodilatation that affects the rest of the body (Gille et al., 2008). When MN is applied over large body surface areas, generalized vasodilation can occur, and some individuals have experienced large reductions in blood pressure and syncope (fainting) as a result (Blenkinsopp et al., 2008). In humans, consumption of 3 to 9 g NA per day (intended for reducing the risk of vascular disease) may lead to "niacin hepatitis", gout, and impaired glucose tolerance within a relative short period (less than one week in some cases) (EMEA, 1998). See also Legemiddelhåndboka [online]; Felleskatalogen [online]. The effects of NA are dose related and reversible on cessation of treatment (EVM, 2003). There are few data available on the safety of nicotinamide. Studies in human diabetic subjects indicate that doses up to 3000 mg/day are not associated with adverse events (Council of Europe, 2008).

http://www.zostrix.com/pages/arthritis_info.asp;
http://bit.ly/mUXRlF

[14] The concentration of MN in the formulated veterinary medicinal product is 2% (EMEA, 1998).

[15] http://www.webmd.com/drugs/drug-5806-methyl+nicotinate.aspx?drugid=5806&drugname=methyl+nicotinate&source=1&pagenumber=6

[16] http://www.bibra-information.co.uk/profile-419.html

7. Assessment

Methyl nicotinate (MN) is a skin irritant in man, in particular producing vasodilatation, which is used on purpose in “rubefacient”, to produce a redness or inflammation for a short period of time, often in lip plumper or other lip products.

General toxicity:
There is still not sufficient data to estimate the effect level (NOEL) for methyl nicotinate (MN).

The safety of nicotinate (NA) has been evaluated by various authorities, including the SCF and the EVM. Flushing has been consistently reported at intakes of 50 mg/day and above (Spies et al., 1938; Sebrell and Butler, 1938, cited in EVM, 2003). If 50 mg/day is taken as a LOAEL and an uncertainty factor of 3 is applied to extrapolate to a NOAEL, a value of 50/3 = 17 mg/day (equivalent to 0.28 mg/kg bw/day in a 60 kg adult) for NA is derived (EVM, 2003). The EVM concludes that “there are insufficient data from human or animal studies to establish a Safe Upper Level (UL) for nicotinic acid”, but that the extrapolated NOAEL is useful as a guidance level for dietary supplements (see below). The SCF established a UL for nicotinate of 10 mg/day (equivalent to 0.167 mg nicotinate/kg bw/day for a 60 kg person), based on occasional flushing as the limiting adverse effect.

Cosmetics:
There is still not sufficient data to estimate the effect level (NOEL) for MN, and hence it is not possible to calculate a margin of safety (MoS) (Council of Europe, 2008).

In an attempt to establish safety guidelines for MN, we have taken 10 mg/day (based on UL for nicotinic acid in humans) as the NOEL (equivalent to 0.167 mg nicotinate/kg bw/day) for occasional flushing as the critical adverse effect. Using 1% MN as an illustrative example, we calculated MoS values for some relevant product categories:
0.14 (body lotion), 2.91 (hair styling products) and 18.6 (lip salve / lipstick). Because the NOEL is from recommended safe upper levels (UL) in humans, a MoS of 10 has been taken to represent a sufficient safety margin.

Although systemic adverse effects of MN are rare, generalized vasodilation can occur in susceptible people when MN if applied over large body surface areas, and as a result, some individuals have experienced large reductions in blood pressure and fainting (Zostrix [online], TransformYourHealth [online]).

Food and dietary supplements:
No safety concern is present at current levels of intake (0.6 µg/capita/day) when MN is used as a flavouring agent (JECFA, 2004; Council of Europe, 2008).

The Expert group on Vitamins and Minerals (EVM, 2003) estimated the maximum intake of niacin equivalents[17] from food and dietary supplements to be 307 mg/day, equivalent to 5.1 mg/kg bw/day (see Annex 3 for calculations).

Medicinal products:
MN is present at concentrations of 0.25% (pain relieving rub cream), 0.5% (external analgesic), and up to 1% (topical vasodilator).[18],[19]
Niacin (nicotinamide and/or NA) dosing varies in clinical trials according to the condition it is being used to treat: 500 mg (macular degeneration) up to 3 g (osteoarthritis) and 6 g (cardiovascular

[17] Niacin equivalents (NE): 60 milligram tryptophan equals 1 mg niacin.
[18] References:
http://www.prescriptiondrug-info.com/Drugs/ArthriCare-Arthritis-Pain-Relieving-Rub/
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=40402#nlm34071-1
http://www.zostrix.com/pages/arthritis_info.asp;
http://bit.ly/mUXRlF
[19] The concentration of MN in the formulated veterinary medicinal product is 2% (EMEA, 1998).

disease). Doses of NA in the range of 375 -2000 mg/ day are found for 2 medicinal products, Niaspan (Abbott) and Tredaptive (MSD) in Norway (Felleskatalogen [online]). It is stated that breastfeeding women should not exceed a dose of 20 mg NA/day.

Total exposure:
We estimated a MoS value of 0.13 for MN (1%) exposure taking into account all cosmetic products, which is far below a sufficient safety limit of 10. This represents an exposure of NA at 78 mg/day, equivalent to 1.3 mg/kg bw/day with a cream containing 1% MN.

By comparison, the contribution from dietary supplements and medicinal products is 307 mg/day (equivalent to 5.1 mg/kg bw/day; Annex 3) and 375 – 2000 mg/day (equivalent to 6.3 -33.3 mg/kg bw/day)[20].

[20] Felleskatalogen [online]

8. Conclusion

There are reported health hazards associated with MN, both local and systemic. When used as a topical "rubefaciant", MN causes local dilatation of superficial vessels in the skin. The Council of Europe (2008) concluded in its last safety report on this substance that "*because of local adverse effects such as oedemas, erythema, and sensibilization, MN should be avoided in cosmetic products*".

Because a NOAEL value for MN is not available, we extrapolated a NOEL of 0.167 mg/kg bw /day for occasional flushing as the limiting adverse effect, assuming close pharmacological relationships between nicotinate and methyl nicotinate. The systemic exposure dose (SED) was calculated using a cream containing 1% MN as an illustrative example.

MoS (body lotion): 0.14
MoS (hair styling products): 2.91
MoS (lip salve /lipstick): 18.6
MoS (overall exposure from cosmetics): 0.13

The following maximum usage limits for MN (%) correspond to a margin of safety of 10 (based on human data):

Body lotion: (1% x 0.14) / 10 = 0.014%
Hair styling products: (1% x 2.91) /10 = 0.29%
Lip salve / lipstick: (1% x 18.6) /10 = 1.86%
Overall exposure from cosmetics: (1% x 0.128) /10 = 0.0128%.

We propose a maximum limit[21] of:
0.3% MN in hair care products
1.5% MN in lip salve / lipstick
MN not allowed in body lotions or other cosmetic products.[22]

Remarks:
Breastfeeding women should not exceed a dose of 20 mg NA/day, as there are concerns for adverse effects in babies (Felleskatalogen [online]). NA is contraindicated in patients with reduced liver function, gastrointestinal disturbances, ulcus disease, arterial bleeding. (Felleskatalogen [online]). Although there is a lack of data for MN, assuming similar pharmacological properties and potential adverse effects for MN and NA (methyl nicotinate is rapidly metabolized to nicotinic acid), a precautionary label for these conditions should be displayed on the package /ingredient list.

[21] "a maximum of 0.3% MN for massaging preparations and shower solutions" was recommended in the MN monograph (Council of Europe, 2008).
[22] Several products are marketed on the internet containing 1% MN or more (see table in Annex 2).

9. References

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10. Annexes

Annex 1A: Toxicity

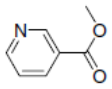
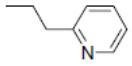
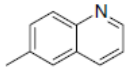
Toxicity

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
mouse	LD	subcutaneous	> 1gm/kg (1000mg/kg)		"Structure et Activite Pharmacodyanmique des Medicaments du Systeme Nerveux Vegetatif," Bovet, D., and F. Bovet-Nitti, New York, S. Karger, 1948Vol. -, Pg. 428, 1948.
mouse	LDLo	parenteral	2gm/kg (2000mg/kg)		"Summary Tables of Biological Tests," National Research Council Chemical-Biological Coordination Center. Vol. 7, Pg. 691, 1955.

http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=Search&actionHandle=getAll3DMViewFiles&nextPage=jsp%2Fcommon%2FChemFull.jsp%3FcalledFrom%3Dlite&chemid=0000093607&formatType=_3D

Annex 1B. Safety evaluation of certain food additives / prepared by the sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA).

Table 1. Summary of the results of safety evaluations of pyridine, pyrrole and quinoline derivatives used as flavouring agents

Flavouring agent	No.	CAS No. and structure	Step 2 Predicted to be metabolized to innocuous metabolites?	Step A3 Does intake exceed the threshold for human intake?[a]	Comments	Conclusion based on current intake
Table 1. (contd)						
Flavouring agent	No.	CAS No. and structure	Step 2 Predicted to be metabolized to innocuous metabolites?	Step A3 Does intake exceed the threshold for human intake?[a]	Comments	Conclusion based on current intake
2-Propionylpyrrole	1319	1073-26-3 	Yes	No Europe: 0.01 USA: 2	See notes 1, 4	No safety concern
Methyl nicotinate	1320	93-60-7 	Yes	No Europe: 0.6 USA: 0.2	See note 6	No safety concern
2-Propylpyridine	1322	622-39-9 	Yes	No Europe: ND USA: 0.9	See note 3	No safety concern
Structural class III						
6-Methylquinoline	1302	91-62-3 	Yes	No Europe: 4 USA: 0.01	See notes 2, 5	No safety concern

CAS: Chemical Abstracts Service; ND: No intake data reported; NR: Not required for evaluation because consumption of the substance was determined to be of no safety concern at step A3 of the Procedure.

[a] The thresholds for human intake for structural classes I, II, and III are 1800, 540 and 90 µg/person per day, respectively. All intake values are expressed in µg/person per day. The combined intake of the flavouring agents in structural class I is 33 µg/person per day in Europe and 11 µg/person per day in the USA. The combined intake of the flavouring agents in structural class II is 103 µg/person per day in Europe and 76 µg/person per day in the USA. The combined intake of the flavouring agents in structural class III is 6 µg/person per day in Europe and 1 µg/person per day in the USA.

Notes:
1 The pyrrole ring undergoes hydroxylation at the C2 position and is excreted in the urine as the corresponding glucuronic acid conjugate.
2 The ring system undergoes hydroxylation at the C3 position and is excreted in the urine as the corresponding glucuronic acid conjugate.
3 Alkyl side-chain oxidation followed by glucuronic acid conjugation and excretion or oxidation to nicotinic acid.
4 The acetyl group is reduced and conjugated with glucuronic acid.
5 Forms a reactive epoxide metabolite that is detoxified through glutathione conjugation.
6 Ester readily undergoes hydrolysis and resulting nicotinic acid is either used in numerous metabolic processes or excreted as the mercapturic acid conjugate.

Reference: JECFA, 2004.

Table 2. Annual volumes of production of pyridine, pyrrole and quinoline derivatives used as flavouring agents in Europe and the USA

Flavouring agent (No.)	Annual volume of production (kg)[a]	Intake[b]		Annual intake from natural occurrence in foods (kg)[c]	Consumption ratio[d]
		µg/day	µg/kg bw per day		
Methyl nicotinate (1320)					
Europe	4	0.6	0.01		
USA	1.8	0.2	0.004	+	NA
2-(3-Phenylpropyl)pyridine (1321)					
Europe	15	2	0.04		
USA[e]	4	0.7	0.01	–	NA
2-Propylpyridine (1322)					
Europe	N/D	N/D	N/D		
USA[e]	5	0.9	0.01	+	NA
Total					
Europe	1005				
USA	648				

NA, not available; N/D, no intake data reported; +, reported to occur naturally in foods (Nijssen et al., 2003), but no quantitative data; –, not reported to occur naturally in foods.

[a] From International Organization of the Flavour Industry (1995) and Lucas et al. (1999) or National Academy of Sciences (1982).

[b] Intake expressed as µg/person per day was calculated as follows: [(annual volume, kg) × (1×10^9 µg/kg)]/[population × survey correction factor × 365 days], where population (10%, 'eaters only') = 32×10^6 for Europe and 26×10^6 for the USA. The correction factor = 0.6 for Europe and 0.8 for the USA, representing the assumption that only 60% and 80% of the annual volume of the flavour, respectively, was reported in the poundage surveys (International Organization of the Flavour Industry, 1995; Lucas et al., 1999; National Academy of Sciences, 1982) or in the anticipated annual volume.
Intake expressed as µg/kg bw per day was calculated as follows: [(µg/person per day)/body weight], where body weight = 60 kg. Slight variations may occur from rounding.

[c] Quantitative data for the USA reported by Stofberg & Grundschober (1987).

[d] The consumption ratio was calculated as follows: (annual consumption in food, kg)/(most recently reported volume as a flavouring agent, kg).

[e] The volume cited is the anticipated annual volume, which was the maximum amount of flavour estimated to be used annually by the manufacturer at the time the material was proposed for use as a flavouring agent. National surveys (National Academy of Sciences, 1970, 1982, 1987; Lucas et al., 1999), if applicable, revealed no reported use as a flavouring agent.

[f] Annual volume reported in previous USA survey (National Academy of Sciences, 1982).

Annex 1C: Acute toxicity

Table 3. Studies of the acute toxicity of pyridine, pyrrole and quinoline derivatives administered orally

No.	Flavouring agent	Species	Sex	LD_{50} (mg/kg bw)	Reference
1301	Indole	Rat	M	1000	Smyth et al. (1962)
1302	6-Methylquinoline	Rat	NR	1260	Moreno (1976)
1303	Isoquinoline	Rat	NR	360	Smyth et al. (1951)
1304	Skatole	Rat	NR	3450	McGee (1974)
1309	2-Acetylpyridine	Rat	NR	2280	Posternak et al. (1975)
1309	2-Acetylpyridine	Rat	M, F	2160[a]	Spanjers & Til (1968)
1310	*N*-Furfurylpyrrole	Mice	F	335	Shellenberger (1971)
1310	*N*-Furfurylpyrrole	Mice	M	580	Shellenberger (1971)
1310	*N*-Furfurylpyrrole	Mice	M, F	380	Moran & Easterday (1980)
1316	3-Acetylpyridine	Rat	M	57[b]	Costello et al. (1992)
1316	3-Acetylpyridine	Rat	F	51[b]	Costello et al. (1992)
1318	5-Ethyl-2-methylpyridine	Rat	NR	1540	Smyth et al. (1951)
1318	5-Ethyl-2-methylpyridine	Rat	NR	368	Izamerov et al. (1982)
1318	5-Ethyl-2-methylpyridine	Mice	NR	282	Izamerov et al. (1982)
1318	5-Ethyl-2-methylpyridine	Rat	M	1195[c]	Myers & Ballantyne (1997)
1319	2-Propionylpyrrole	Mice	M, F	1620	Moran & Easterday (1980)
1320	Methyl nicotinate	Mice	NR	2800	Pellmont (1977)

F, female; M, male; NR, not reported.

[a] Calculated using density = 1.08 g/ml (Sigma-Aldrich, 2003; available from http://www.sigmaaldrich.com).

[b] Calculated using density = 1.102 g/ml (Sigma-Aldrich, 2003; available from http://www.sigmaaldrich.com).

[c] Calculated using density = 0.919 g/ml (Sigma-Aldrich, 2003; available from http://www.sigmaaldrich.com).

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Annex 3: Exposure assessment – niacin in food

The exposure data below for intake from food are for niacin equivalents. These are defined as the niacin content of the food plus 1/60th the content of tryptophan, as nicotinic acid is formed in the body from the metabolism of tryptophan. It is not possible to distinguish the two forms of niacin in this survey data.

Food:
Mean: 34 mg/day (from 1986/87 NDNS; UK National Diet and Nutrition Survey)
97.5th percentile: 57 mg/day

Supplements:
up to 250 mg/day (as nicotinamide, or up to 150 mg/day as nicotinic acid).
Reference: OTC Directory 2001-2002. The Proprietary Association of Great Britain, Communications International Group, London.

Total food /supplements: estimated maximum intake of niacin equivalents: 57 + 250 = **307 mg/day**

No potential high intake groups have been identified.