ANSES Opinion
Request No 2016-SA-0209

The Director General

Maisons-Alfort, 23 February 2018

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the risks associated with the consumption of food supplements containing melatonin

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 23 February 2018 shall prevail.

On 27 September 2016, ANSES issued an internal request to conduct an expert appraisal on the following issue: risks associated with the consumption of food supplements containing melatonin.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Melatonin is a hormone secreted by the pineal gland during the night. Its physiological function is to provide the body, the brain in particular, with information on the nychthemeron, thus promoting sleep. Many food supplements containing melatonin have appeared on the French market. They are very popular, with an estimated 1.4 million packs per year being sold[1].

Between the establishment of its nutrivigilance scheme and May 2017, ANSES received 90 reports of adverse effects likely to be associated with the consumption of food supplements containing melatonin. Nineteen of these reports contained enough information to be analysed for their causality.

In this context, ANSES issued an internal request with a view to identifying the potential health risks, but not the possible effectiveness, of food supplements containing melatonin. This opinion is based on the adverse effects reported to ANSES and likely to be associated with the consumption of food supplements containing melatonin.

[1] Estimate provided by the French Food Supplements Association (SYNADIET) based on data collected in March 2016 by IMS Health for the "pharmacy and drug store" sector, and by IRI for the "supermarkets and hypermarkets" sector.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

This expert appraisal falls within the scope of the Expert Committee (CES) on "Human Nutrition". It was conducted by the Working Group (WG) on "Nutrivigilance". The methodological and scientific aspects of the work were presented to the CES on 9 November 2017 and 7 December 2017. It was adopted by the CES at its meeting on 12 January 2018.

ANSES considers interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

The 90 reports of adverse effects likely to be associated with the consumption of food supplements containing melatonin were collected in the framework of the nutrivigilance scheme. These reports were submitted by healthcare professionals, the French National Agency for Medicines and Health Products Safety (ANSM), the regional pharmacovigilance centres (CRPV), and by manufacturers of food supplements containing melatonin. Nineteen reports underwent a causality analysis, carried out using the method developed by ANSES (2011), while the others were regarded as incomplete (dates of consumption unknown, products not clearly identified, etc.).

ANSES's Health Monitoring and Alerts Department was asked to question the French poison control centres (CAPs) and the national toxicovigilance network about any adverse effects involving melatonin that had been brought to their attention. The results of this enquiry were submitted in the form of a report, which has been summarised in Section 3.2.3.

ANSES contacted other health agencies in the European Union, Canada and the United States to obtain any insights they may have gained from surveillance and expert appraisals on the safety of food supplements containing melatonin. The responses provided have been summarised in Section 3.2.4.

The French Food Supplements Association (SYNADIET) was consulted with a view to asking its members to provide ANSES with any information they deemed relevant.

Lastly, an analysis of the literature data was conducted with regard to any adverse effects observed in the context of nutrivigilance. To do this, each adverse effect detailed in the reports, whether or not they had undergone an analysis, was cross-checked with the term "melatonin" using the Scopus literature search engine.

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES

3.1. Melatonin

3.1.1. Regulatory status and claims

In France, melatonin has been included on List II of poisonous substances intended for human medicine[2] since 2011. In 2007, the pharmaceutical product Circadin® obtained marketing authorisation in several European countries, including France. This medicinal product is a prolonged-release formulation containing 2 mg of synthetic melatonin. It is indicated "*as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over*" (Vidal 2017). This product also benefits from a Temporary Recommendation for Use (RTU)[3] for children over 6 years of age, in disturbances of the sleep-wake cycle related to behavioural disorders (Rett, Smith-Magenis and Angelman syndromes, tuberous sclerosis complex and autism spectrum disorders), at a dose of 4 to 6 mg per day.

Melatonin may also take the form of extemporaneous preparations, without any dose limit or age restriction.

In 2015, the dose of 1 mg per dosage unit of melatonin was exempted from the regulations on poisonous substances by a Ministerial Order[4], which was annulled by the Council of State on 31 March 2017[5]. Food supplements containing less than 2 mg of melatonin per dose are currently authorised by administrative decision of the DGCCRF[6].

According to the information collected in 2017 from EFSA's European focal points[7], the regulatory status of melatonin varies according to the states:

- In Latvia, it is authorised in food supplements below 2 mg per dose and per day;
- In Cyprus, Croatia, Spain, Greece, Italy and Poland it is authorised in food supplements up to 1 mg per dose and per day;
- In Belgium, products containing 0.3 mg of melatonin or more per dose and per day are considered medicinal products by function[8];

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[2] Ministerial Order of 23 September 2011 on inclusion on lists of poisonous substances, which led to melatonin being removed from List I of poisonous substances (where it had been included since the Ministerial Order of 26 March 2009) and added to List II.

[3] Article L. 5121-12-1 of the French Public Health Code, resulting from the Act of 29 December 2011 and amended by the Act of 8 August 2014 amending social security funding for 2014, enables the French Health Products Safety Agency (ANSM) to draft a Temporary Recommendation for Use (RTU) authorising the prescription of a pharmaceutical product with a marketing authorisation (MA) in France, for an indication or under conditions of use not consistent with its MA. It is an exceptional derogation procedure, with a limited duration of three years, renewable.

[4] Ministerial Order of 8 September 2015 amending the Ministerial Order of 22 February 1990 on exemption from the regulations on poisonous substances intended for human medicine.

[5] Decision No. 397644 of 31 March 2017 of the Council of State in its judicial capacity.

[6] List of substances for nutritional or physiological purposes conditionally eligible for Article 15: https://www.economie.gouv.fr/files/files/directions_services/dgccrf/securite/teleicare/table-sbnp-sous-conditions.pdf (accessed on 11 October 2017).

[7] List of EFSA focal points: http://www.efsa.europa.eu/en/people/fpmembers (accessed on 11 October 2017).

- In Germany, products containing 0.28 mg of melatonin or more per dose and per day are considered medicinal products by function;
- Melatonin is not authorised in food supplements in Denmark, the Czech Republic, the United Kingdom, Slovenia or Switzerland.

In Canada, melatonin has been approved as an ingredient of natural health products. In the United States, irrespective of its dosage, melatonin is regarded as an ingredient of food supplements.

EFSA has issued a favourable opinion for two claims relating to the presence of melatonin in foodstuffs (Commission Regulation (EU) No 432/2012):

- "*Melatonin contributes to the alleviation of subjective feelings of jet lag*". This claim may be used only for *food which contains at least 0.5 mg of melatonin per quantified portion.* In order to bear the claim, information shall be given to the consumer that the beneficial effect is obtained with a minimum intake of 0.5 mg to be taken close to bedtime on the first day of travel and on the following few days after arrival at the destination;
- "*Melatonin contributes to the reduction of time taken to fall asleep*". This claim may be used only for *food which contains 1 mg of melatonin per quantified portion.* In order to bear the claim, information shall be given to the consumer that the beneficial effect is obtained by consuming 1 mg of melatonin close to bedtime.

3.1.2. Characterisation and endogenous secretion of melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that was discovered in 1958. It has an indole structure, is neutral, and lipophilic at physiological pH (Claustrat 2009). It is synthesised by the body in two steps from serotonin resulting from the transformation of tryptophan (see Figure 1) (Welford *et al.* 2016). The mRNA encoding the enzymes arylamine-*N*-acetyl-transferase (AANAT) and hydroxyindole-*O*-methyl-transferase (HIOMT) are expressed according to a circadian rhythm in the pineal gland (Claustrat, Brun, and Chazot 2005).

[8] Directive 2004/27/EC defines a medicinal product by function as "any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis".

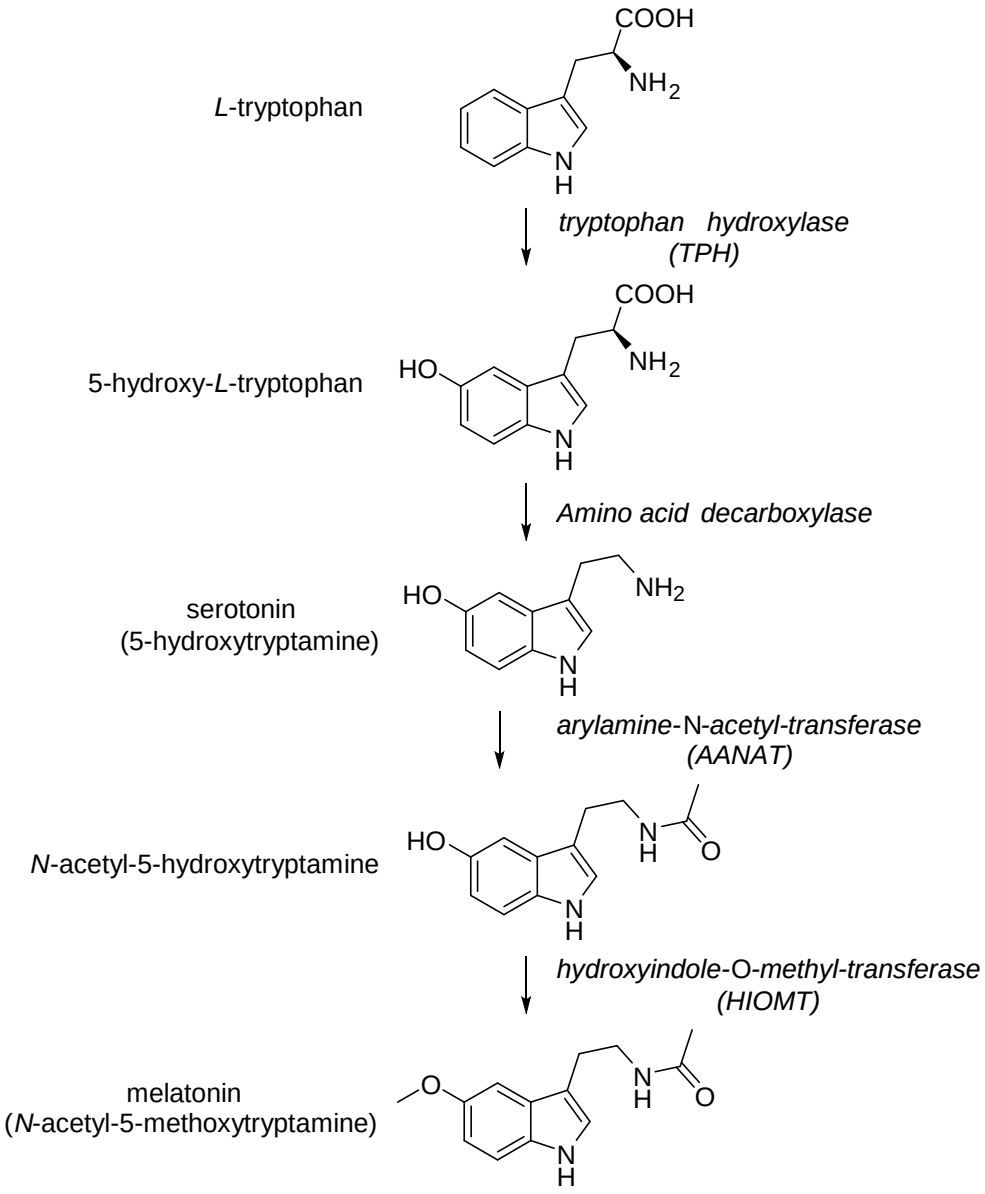

Figure 1: Biosynthesis of melatonin

Melatonin is mainly secreted by the pinealocytes of the pineal gland, and incidentally by the retina, intestine, skin, platelets and bone marrow (Singh and Jadhav 2014). This secretion occurs preferentially at night and over a duration of around ten hours. The maximum concentration is reached on average at around 3:00 to 4:00 in the morning. In adults, diurnal and nocturnal blood concentrations of melatonin are around 10 and 60 pg/mL, respectively (Comai and Gobbi 2014). Diurnal concentrations are low, and even undetectable, in blood (Claustrat 2009). The plasma profile of melatonin has considerable interindividual variability. On the other hand, it is highly reproducible from one day to another in the same individual. Lastly, exogenous administration of a dose as low as 1 mg leads to supraphysiological concentrations (> 100 pg/mL) (Claustrat 2009).

3.1.3. Pharmacokinetic data

- **Absorption and bioavailability of melatonin after oral administration**

The summary of product characteristics (SPC)[9] for the medicinal product Circadin®, containing 2 mg of melatonin released gradually, indicates that absorption of ingested melatonin is complete in adults but may be decreased by up to 50% in the elderly. Bioavailability is in the order of 15% due to a significant first-pass effect through the liver. Peak concentration in the blood (1020 pg/mL) is obtained 3 hours after administration (Vidal 2017).

For forms without controlled release, this time varies between 15 and 90 minutes depending on the dose studied (2 mg and 25 mg, respectively). Oral bioavailability was measured at between 9% and 33% for doses between 0.3 mg and 100 mg (Harpsøe *et al.* 2015).

The sublingual form significantly increases the peak concentration, probably by avoiding the first pass through the liver (Bartoli *et al.* 2012).

- **Distribution**

After passing into the bloodstream, melatonin is able to bind 50-60% to plasma proteins (albumin and α1-acid glycoprotein), as well as to high-density lipoproteins (Cardinali, Lynch, and Wurtman 1972, Morin *et al.* 1997, Vidal 2017). Melatonin crosses the blood-brain barrier to exert its effect on the central nervous system (Claustrat 2009). From the bloodstream, it is also distributed in tissues, cellular compartments and biological fluids (saliva, bile, synovial fluid, urine, cerebrospinal fluid, seminal fluid, amniotic fluid and breast milk) (Claustrat, Brun, and Chazot 2005, Acuña-Castroviejo *et al.* 2014).

- **Metabolism and excretion**

Melatonin is metabolised primarily in the liver (90% of circulating melatonin), where it is hydroxylated to 6-hydroxymelatonin by the isoenzymes CYP1A1, CYP1A2, CYP1B1 or CYP2C19 (Ma *et al.* 2005, Vidal 2017). The 6-hydroxymelatonin is then mainly sulphoconjugated to a metabolite that is fully excreted in the urine within 12 hours of ingestion. Around 1 to 2% of melatonin is excreted directly in the urine, in unchanged form (Claustrat, Brun, and Chazot 2005, Singh and Jadhav 2014, Vidal 2017).

In the brain, melatonin is oxidised to N_1-acetyl-N_2-formyl-5-methoxykynuramine (AFMK). This compound is derived from the reaction of melatonin with reactive oxygen species (ROS) and has antioxidant properties *in vitro* (Singh and Jadhav 2014).

The elimination half-life of melatonin after oral administration varies from 32 minutes (for a dose of 2 mg) to 126 minutes (for a dose of 4 mg) (Harpsøe *et al.* 2015).

[9] The SPC for Circadin® is available from the website of the European Commission at the following address: http://ec.europa.eu/health/documents/community-register/2014/20140627129116/anx_129116_en.pdf

- **Regulation**

The melatonin secretion rate is controlled by an internal clock located in the suprachiasmatic nuclei of the hypothalamus. The alternation between light/dark is the main factor regulating melatonin secretion. The reduction in light causes the release of noradrenaline, which interacts with the post-synaptic β1 and α1 adrenergic receptors of the pinealocytes. As a consequence, cAMP synthesis increases, which in turn increases serotonin *N*-acetyltransferase (NAT) activity and leads to the synthesis of melatonin in the pinealocytes. High melatonin production is maintained during the dark phase of the nychthemeron, as long as the subject is not exposed to light. Indeed, in the presence of light, noradrenaline secretion is inhibited (Claustrat 2009, Cipolla-Neto *et al.* 2014, Singh and Jadhav 2014).

When melatonin is administered in the afternoon or evening, a phase advance is observed (the peak of melatonin secretion occurs earlier), with a sedative effect causing an increase in feelings of tiredness, a slower reaction time and a decrease in sleep latency (Claustrat 2009). In contrast, administration in the morning or at noon leads to a phase delay, which is smaller or may even be absent. The phase delay effect is less pronounced than the phase advance effect. The effect changes direction at around 15:00 (phase delay effect for administration before 15:00, phase advance effect after 15:00). This time marker is modulated by the subject's chronotype.

3.1.4. Physiology/pharmacodynamic data

In humans, melatonin exerts its effect by interacting with two receptor sub-types, MT1 and MT2, which are transmembrane G protein-coupled receptors. They are expressed alone or co-expressed in the tissues, particularly in the central nervous system where they are found in the suprachiasmatic nuclei, retina, hippocampus, cerebellum and central dopaminergic system (Ekmekcioglu 2006). At the peripheral level, the MT1 receptors are expressed in the ovaries, testes, mammary glands, gall bladder, liver, kidney, lungs, thyroid gland, skin, adipose tissue, skeletal muscle, bone marrow, and the cardiovascular and immune systems. The MT2 receptors are expressed in the retina, thymus, lungs, ovaries, stomach, duodenum, colon and pancreas (Singh and Jadhav 2014, Lardone *et al.* 2014).

The effects of melatonin on sleep result from the activation of receptors in the suprachiasmatic nuclei. Activation of the MT1 receptors inhibits the neuronal activity of the suprachiasmatic nuclei. Among diurnal species such as humans, this inhibition reduces the biological clock's activator effects on vigilance, which increases drowsiness and the tendency to sleep (Ekmekcioglu 2006). Activation of the MT1 receptors is therefore responsible for the "hypnotic" effects of melatonin. Activation of the MT2 receptors, in contrast, has a dominant role in phase-shifting the circadian rhythm of the neuronal activity of the suprachiasmatic nuclei (Dubocovich *et al.* 2010).

The MT1 and MT2 receptors may have opposing functions on different tissues or organs and complementary functions from a physiological point of view. For example, it has been shown that the MT1 and MT2 receptors act in an opposing way on the vascular system, producing respectively vasoconstriction and vasodilation (Comai and Gobbi 2014). The lowering of body temperature induced by melatonin, which may contribute to enhancing sleepiness (Vidal 2017), may be a consequence of its vasoconstrictor effect from the activation of MT1 receptors.

Quinone reductase 2 (QR2) has been described as the assumed MT3 receptor (Nosjean *et al.* 2000). This enzyme, found in different tissues and structurally unrelated to the MT1 and MT2 receptors, may play a detoxification role and could participate in the regulation of intraocular pressure, but its exact effects and their impact are still little known (Emet *et al.* 2016).

In addition to its effects on the biological clock, melatonin has other physiological properties: modulation of mood, sexual behaviour or the immune system, regulation of body temperature or blood pressure. These effects are based firstly on a broad distribution of MT1 and MT2 receptors,

and secondly on the pharmacological effects of melatonin, independent from the MT1 and MT2 receptors and involving the binding site MT3 (Singh and Jadhav 2014, ANSES 2016).

3.2. Adverse effects of melatonin

3.2.1. Cases from nutrivigilance

Between the establishment of the nutrivigilance scheme in 2009 and the month of May 2017, ANSES received 90 reports of adverse effects likely to be associated with the consumption of food supplements mainly containing melatonin.

The most frequently reported effects were general symptoms (headaches, dizziness, drowsiness) and neurological (tremors, migraine), digestive (nausea, vomiting, abdominal pain) and psychological (nightmares, irritability) disorders.

Among these 90 reports, 19 were analysed for their causality, based on the method defined in ANSES's Opinion of 11 May 2011 (ANSES 2011) (see Tableau 1), by the Working Group on "Nutrivigilance", while the others contained insufficient documentation to be analysed (due for example to the dates of consumption being unknown or the consumed product not being identified).

Two of these 19 cases involved melatonin being taken in the context of a suicide attempt. In these cases, the melatonin dose consumed largely exceeded that recommended by the manufacturers (misuse with overdose) and was combined with other food supplements or medicinal products.

Table 1: Analysable cases received by the nutrivigilance scheme between 2009 and May 2017

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2013-109	Somniphyt® 30 Melatonin[14] (Santé Verte)	F, 40 years	serotonin syndrome (agitation, hallucination, excessive perspiration) 3 hours 1.9 mg	neurology	3	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	combined with: venlafaxine (antidepressant) food supplement containing several substances with serotonergic activity

[10] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).
[11] The chronological score ranges from C0 to C4.
[12] The semiological score ranges from S0 to S3.
[13] The intrinsic score ranges from I0 (excluded) to I4 (very likely).
[14] Composition of Somniphyt 30® Melatonin (marketed before May 2016): melatonin, *Griffonia simplicifolia*, magnolia, valerian, California poppy, L-tryptophan, L-glutamine, St John's wort, vitamin B6

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2014-016	Valdispert Mélatonine Nuit Paisible®[15] (Vemedia Pharma)	M, 43 years	spasms, tremor a few hours 1 mg	neurology	1	C3 (timeframe consistent, progression suggestive)	S1 (another possible aetiology)	likely	epileptic person treated with Keppra®
2016-341	Melatonyl®[16] (Arkopharma)	F, 51 years	memory disorders unknown dose	neurology	1	C0 (timeframe inconsistent)	-	responsibility excluded	person with bipolar disorders and depression combined with: Lysanxia®, Depakote®, Atarax® and Deroxat®
2016-195	Somniphyt® 30 Melatonin (Santé Verte)	F, 50 years	trembling in the legs and palpitations about 30 minutes 3.8 mg	neurology and cardiovascular	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	no history combined with: Cerazette®

[15] Composition of Valdispert Mélatonine Nuit Paisible®: melatonin, vitamin B6, magnesium, zinc
[16] Composition of Melatonyl®: melatonin

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2016-194 (attempted suicide)	Somniphyt® 30 Melatonin (Santé Verte)	F, 37 years	bradycardia and drowsiness unknown time 57 mg	cardiovascular and general symptoms	3	C3 (timeframe consistent, progression suggestive)	S0 (other aetiology very probable)	possible	psychiatric history combined with: Lysanxia®, Deroxat®, Donormyl® and alcohol
2016-192 (attempted suicide)	Somniphyt® 30 Melatonin (Santé Verte)	F, 31 years	tachycardia about 30 minutes 57 mg	cardiovascular	1	C3 (timeframe consistent, progression suggestive)	S0 (other aetiology very probable)	possible	history of cardiovascular diseases combined with: Donormyl® and Baraclude®
2017-040	Novanuit®[17] (Sanofi)	F, 57 years	digestive disorders and palpitations 1 hour unknown dose	digestive and cardiovascular	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	no associated consumption identical symptoms with Temesta®, Doliprane® and trimebutine
2016-117	Somniphyt® 30 Melatonin (Santé Verte)	F, 37 years	acute pancreatitis about 3 months 1.9 mg/day	digestive	2	C2 (timeframe not very consistent, progression suggestive)	S2 (a few aetiologies explored and excluded)	possible	person with a sarcoidosis and a factor V deficiency combined with: Biomag®, Mag2® and rhodiola

[17] Composition of Novanuit®: melatonin, passionflower, California poppy, lemon balm, vitamin B6

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2016-042	Govital Méla-sommeil®[18] (Urgo)	F, 51 years	discomfort and vomiting 3 hours 1 mg	general and digestive symptoms	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	no associated consumption
2014-464	Novanuit® (Sanofi)	F, 33 years	myalgia, abdominal pain several hours 0.5 mg	rheumatology and digestive	1	C3 (timeframe consistent, progression suggestive)	S2 (a few aetiologies explored and excluded)	likely	no history no associated consumption
2017-068	Granions Somdor+ Melatonin®[19] (Granions)	F, 56 years	cramps, arthralgia 30 minutes 1 mg	rheumatology	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	no history combined with: Oestrodose® and progesterone

[18] Composition of Govital Méla-sommeil®: melatonin, passionflower, lemon balm, chamomile
[19] Composition of Granions Somdor+ Melatonin®: melatonin, hawthorn, passionflower, hops, valerian

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2015-338	Valdispert Melatonin Bonne Nuit®[20] (Vemedia Pharma)	F, 89 years	balance disorders several hours 4.5 mg	general symptoms	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	history of ischaemic heart disease combined with: aspirin, amlodipine, allopurinol, simvastatin and candesartan
2016-298	Novanuit® (Sanofi) Valdispert Melatonin État de Fatigue®[21] (Vemedia Pharma)	F, 62 years	headaches a few hours 1 mg	general symptoms	1	C4 (timeframe consistent, progression suggestive, reintroduction positive)	S1 (no aetiology sought)	likely	combined with: Levothyrox®, valsartan and simvastatin
2013-081	Somniphyt® 30 Melatonin (Santé Verte)	M, 76 years	burning mouth, redness in the throat 3 days 1.9 mg/day	otorhinolaryngology	1	C4 (timeframe consistent, progression suggestive, reintroduction positive)	S1 (no aetiology sought)	likely	combined with: allopurinol, lercanidipine, aspirin and tramadol/paracetamol

[20] Composition of Valdispert Melatonin Bonne Nuit®: melatonin
[21] Composition of Valdispert Melatonin État de Fatigue®: melatonin, magnesium, zinc, vitamin B6

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2015-341	Novanuit® (Sanofi)	M, 87 years	nightmares a few hours 1 mg	psychological	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	likely	person with prostate cancer combined with: Zopiclone®, Casodex® and Enantone®
2014-105	Melatonin®[22] (Solgar)	M, 46 years	anaphylactic shock 10 minutes 1 mg	allergy	3	C2 (timeframe consistent, progression cannot be interpreted)	S1 (no aetiology sought)	possible	no history no known allergy
2015-180	Novanuit® (Sanofi)	F, 64 years	pruritus, blotches on the body and scalp 15 days unknown dose	dermatology	2	C2 (timeframe consistent, progression cannot be interpreted)	S1 (no aetiology sought)	possible	no history no associated consumption
2015-351	Novanuit® (Sanofi)	F, 60 years	hepatic cytolysis about 2 days 1 mg/day	hepatology	2	C2 (timeframe consistent, progression cannot be interpreted)	S2 (a few aetiologies explored and excluded)	possible	person monitored for autoimmune hepatitis combined with: Meteospasmyl®, Transipeg®, Zomigoro® and ZymaD®

[22] Composition of Melatonin®: melatonin

Registration number	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) Onset time Melatonin dose ingested	Type(s) of adverse effect(s)	Level of severity of the clinical picture[10]	Chronological score[11]	Semiological score[12]	Intrinsic causality[13]	Comments
2016-322	Melatonin Valerian®[23] (Vitarmonyl)	F, 46 years	allergic nephritis, acute renal failure about 15 days 3 or 4 mg/d	uro-nephrology	2	C2 (timeframe consistent, progression cannot be interpreted)	S0 (other aetiology very probable)	doubtful	person with ankylosing spondylitis history of pyelonephritis and urinary tract infections combined with: diclofenac and piroxicam

[23] Composition of Melatonin Valerian®: melatonin, valerian

The breakdown of the analysed cases by type of effect is shown in Figure 2 (some products may have caused several different adverse effects).

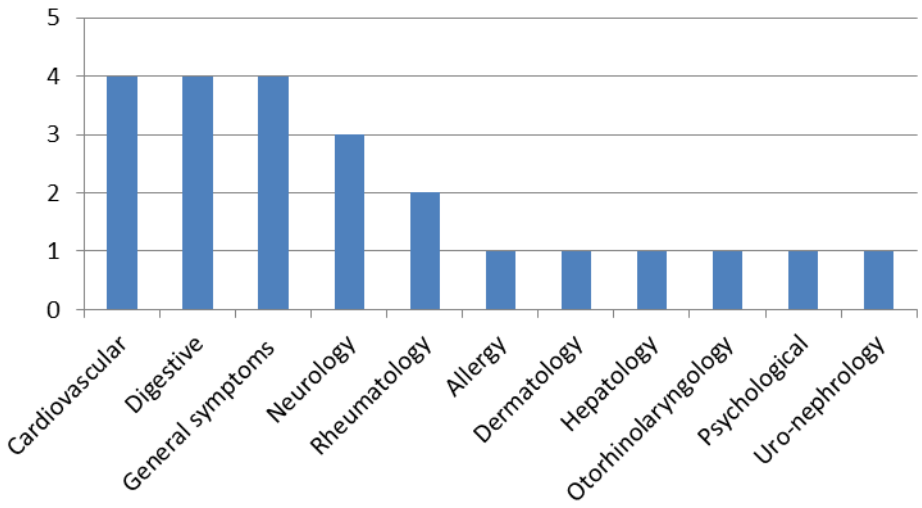

Figure 2: Breakdown of types of adverse effects in nutrivigilance for melatonin (analysable cases)

For these analysable cases, the most frequently reported effects were general symptoms (headaches, drowsiness, dizziness) and effects of a cardiovascular, digestive and neurological nature. Causality was considered likely in 11 cases. The severity[24] of these 11 cases was Level 1, except for the case of serotonin syndrome, whose severity was Level 3.

Melatonin was rarely the only ingredient present in the composition of the food supplements involved in these cases. The role of another food supplement ingredient in the onset of the adverse effect cannot therefore be ruled out.

In addition, the occurrence of the adverse effects could have been facilitated by interactions between the different components of the food supplement or between the food supplement and any medicinal products consumed concomitantly.

3.2.2. Cases from pharmacovigilance

The ANSM collected more than 200 cases of adverse effects likely to be associated with the consumption of melatonin (in the form of a medicinal product, extemporaneous preparation or food supplement), between 1985 and December 2016. The cases involving food supplements (9 cases) were registered in the nutrivigilance database and analysed when they were sufficiently documented. Forty-three percent of the adverse events reported to the pharmacovigilance scheme were neurological (syncope, drowsiness, headaches, convulsions). The other most frequently reported adverse effects were psychological (anxiety, depressive disorders), corresponding to 24% of reports, and dermatological (rash, maculopapular rash) and digestive (vomiting, constipation, acute pancreatitis), each accounting for 19% of reports.

[24] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).

3.2.3. Cases from toxicovigilance

Between 1 January 2010 and 30 November 2016, 46 cases of adverse effects likely to be associated with the consumption of food supplements containing melatonin were registered in the national database of poisoning cases in the CAPs' information system.

Of these 46 cases, 26 concerned melatonin taken in the framework of a suicide attempt.

For the remaining 20 cases, 11 occurred due to the consumption of melatonin alone. Of these 11 cases, eight involved consumption of melatonin at the recommended dose. The adverse effects reported were two cases of headaches, one case of paraesthesia and dizziness, three cases of tachycardia, one case of skin erythema, one case of asthenia and pain in the right hypochondrium, and one case of convulsions (appearing in a context of alcohol withdrawal).

In the cases where the dosage was not respected, consumption ranged from 10 to 12 mg/d. The reported effects were nausea, vomiting, dizziness and drowsiness.

Lastly, the symptoms reported for the nine cases where melatonin was taken in combination with other products (particularly neuroleptic or antipsychotic drugs) were headaches, nausea, visual hallucinations, balance disorders, drowsiness, extrapyramidal syndrome and arterial hypotension. Eight of the consumers were receiving treatment for psychiatric disorders.

3.2.4. Cases identified abroad

3.2.4.1. In Europe

In November 2016, ANSES approached its European counterparts with a view to obtaining more data on the adverse effects likely to be associated with the consumption of food supplements containing melatonin. Several countries responded that no adverse effects had been brought to their attention with this type of product (Austria, Belgium, Croatia, Cyprus, Denmark, Greece, Latvia, Lithuania, Slovakia, Spain and the United Kingdom). Some of these countries (such as Belgium) only authorise doses far lower than those used in France, or do not authorise food supplements containing melatonin at all (United Kingdom, Denmark). Moreover, most European countries do not have a nutrivigilance scheme, and adverse effects likely to be associated with the consumption of food supplements are not collected systematically. For the countries that submitted data, the melatonin dose behind the adverse effects was not always known.

In Finland, two reports of adverse effects (difficulty falling asleep and sleepwalking) occurring after the consumption of food supplements containing 1 mg of melatonin have been notified since 2013.

In Italy, 19 reports of adverse effects were recorded between January 2002 and October 2016; these effects included headaches, dizziness, convulsions, skin rashes and discomfort.

Several adverse effects have been reported (unknown number, frequency and dose of melatonin) in other Member States:

- diarrhoea, agitation and headaches in the Netherlands;
- asthenia, dizziness, confusion, abnormal gait and vomiting in Poland.

In Germany, the pharmacovigilance scheme identified 63 cases of adverse effects likely to be associated with the consumption of medicinal products containing melatonin. The reported symptoms were tachycardia, agitation, elevated transaminases, nausea, headaches, drowsiness, eyesight disorders, nightmares and suicidal thoughts. Among these cases, 12 suicide attempts with melatonin alone or combined with other medicinal products were reported.

3.2.4.2. In the United States and Canada

ANSES also approached the FDA (Food and Drug Administration) in the United States and Health Canada.

In Canada, melatonin has been approved as an ingredient of natural health products. It is used to promote sleep. The adverse effects potentially associated with this substance are grouped in Canada Vigilance's online database of adverse effects. Health Canada forwarded to ANSES details of 102 cases of adverse effects, recorded between 1995 and June 2016. The most frequently reported effects were general symptoms (dizziness, headaches, fatigue, drowsiness), followed by neurological effects (impaired consciousness, muscle spasms), and digestive (abdominal pain, nausea, diarrhoea, vomiting), psychological (nightmares, anxiety, irritability) and cardiovascular (tachycardia, palpitation, hypertension) disorders.

The FDA did not send any data within the requested timeframe.

The adverse effects collected in the nutrivigilance, pharmacovigilance and toxicovigilance schemes, and from the vigilance schemes of other European countries and Canada, are heterogeneous in nature. They mainly concern general symptoms, and neurological, cardiovascular, digestive, psychological and dermatological effects.

3.2.5. Literature data

3.2.5.1. Data on oral toxicology in animals (EMA 2007)

- **Acute toxicity**

The median lethal dose (LD_{50}) is 1250 mg/kg in mice and more than 3200 mg/kg in rats.

- **Toxicity after repeated administration**

After repeated administration of melatonin in rats (13 or 26 weeks) and dogs (6 months), toxic effects were observed on the liver (hypertrophy) and the genital tract (adenomyosis). These effects were observed from 75 mg/kg/day in rats. The EMA concluded that these effects occurred after exposure to doses far above the therapeutic doses in humans.

No new data have been identified that alter the conclusions of the EMA.

- **Genotoxicity and carcinogenicity**

In vitro (Ames test, gene mutation and chromosomal aberration on mammalian cells) and *in vivo* (micronuclei) tests showed that melatonin has no mutagenic, clastogenic or aneugenic effect. No structural damage was detected *in silico* for its main metabolite, 6-hydroxymelatonin.

The carcinogenic potential of melatonin was assessed in rats. An increase in thyroid tumours was observed at the highest doses in the study. This carcinogenic potential has not been completely elucidated and requires additional mechanistic data.

Given that no genotoxic properties have been identified for melatonin, that the exposure doses in rats were significantly higher than those expected in humans and that taking melatonin for long periods is not recommended, the EMA concluded that the risk of carcinogenicity to humans is minimal.

Since 2007, numerous *in vivo* and *in vitro* experimental data have been published on the oncostatic effect of melatonin on different tumours (breast, prostate, colorectal cancer, etc.) (Reiter *et al.* 2017).

No new data have been identified that alter the conclusions of the EMA.

➢ **Reprotoxicity and effect on fertility**

Studies on reproduction and development, taken into account in the EMA's assessment of Circadin®, show a toxic effect of melatonin on embryo-foetal development in rabbits and on postnatal development in rats. These results led the EMA to advise against melatonin intake by pregnant and breastfeeding women.

The new data available in the literature on animals do not alter the conclusions of the EMA (Singh *et al.* 2013).

➢ **Breastfeeding**

The SPC for Circadin® mentions that "*there are data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Therefore, breastfeeding is not recommended in women under treatment with melatonin*" (Vidal 2017).

3.2.5.2. Adverse effects in humans reported in the literature

A literature search was conducted for adverse effects reported in nutrivigilance in order to observe their frequency of occurrence and the melatonin doses at which they appeared. This search was only performed on the ingredient "melatonin" and not on the other ingredients associated with it in the food supplements involved. In this section, the different types of effects are presented in decreasing order of frequency of occurrence in nutrivigilance.

➢ **General symptoms**

The reports received under the nutrivigilance scheme and describing adverse effects categorised as "general" concerned one case of discomfort, one case of headaches and one case of balance disorder. For each of these, causality was considered likely. Causality was considered possible with one case of drowsiness, but it concerned a misuse with overdose (suicide attempt).

These different adverse effects have been reported in the scientific literature, mainly during clinical trials to assess the efficacy and safety of melatonin.

- **Headache**

Buscemi *et al*. (2005 and 2006) conducted two meta-analyses of the clinical data on the efficacy and safety of melatonin administered for primary[25] and secondary[26] sleep disorders. For the meta-analysis relating to primary sleep disorders, 10 studies involving approximately 222 participants were selected for the safety analysis. The doses of melatonin implicated in these studies were not

[25] Primary sleep disorders cannot be attributed to any medical, psychological or environmental cause. They have a physiological origin that directly affects the mechanisms producing sleep.

[26] Secondary disorders are sleep disorders associated with other conditions: neurological disorders or substance abuse, for example.

specified. For the meta-analysis on the secondary disorders, seven studies were selected, involving 164 participants. The doses of melatonin administered were between 0.5 and 10 mg. The adverse effects most often described were headaches, dizziness and nausea, but there was no significant difference in the occurrence of these effects between the groups receiving melatonin or a placebo. The authors therefore concluded that there were no adverse effects associated with short-term administration of melatonin (3 months) in this range of doses, but considered that the data on long-term toxicity were insufficient (Buscemi *et al.* 2005, Buscemi *et al.* 2006).

Seabra *et al.* (2000) conducted a study to assess the toxicity of melatonin administered for 28 days to 30 healthy volunteers, at a dose of 10 mg/d. Ten other participants received a placebo. In the group receiving melatonin, 14 people (47%) presented with headaches. The same symptom was reported in the placebo group by three out of 10 people (30%), leading to a non-significant difference between the two groups.

Van Geijlswijk *et al.* (2011) conducted a follow-up study whose objective was to assess the efficacy and safety of long-term melatonin treatment in prepubertal children with chronic sleep disorders. The average duration of melatonin treatment was around three years at an average dose of 2.69 mg/d (from 0.3 mg/d to 10 mg/d). Thirty-eight per cent of these children reported having regular headaches. Two cases (4%) of weight gain were also reported. The study did not include a control group and the doses of melatonin received by the children with these adverse effects were not specified.

The occurrence of headaches has been reported in other publications where the melatonin doses were between 2 mg/d and 10 mg/d (Smits *et al.* 2001, Campos *et al.* 2004, EMA 2007, Hoebert *et al.* 2009, Costello *et al.* 2014, Xu *et al.* 2015). For these studies, either no data on the significance of the occurrence of this effect were available, or this occurrence was not significant. The vasodilatory action of melatonin has been put forward as the mechanism responsible for this effect (Claustrat 2009).

- **Sleepiness/fatigue**

A randomised placebo-controlled study examining the effects of 3 mg/d of melatonin taken for four months on sleep, mood and hot flushes in post-menopausal breast cancer survivors reported cases of fatigue and sleep disorders. Four out of the 48 participants in the group treated by melatonin (8%) withdrew from the trial because of these adverse effects (Chen *et al.* 2014). No statistical analysis was performed of the relative occurrence of these effects between the treated group and the placebo group.

In the study by Seabra *et al.* (2000), cited above, 17 cases of sleepiness were reported as an adverse effect in the group of 30 people (57%) treated with 10 mg/d of melatonin for 28 days. Six out of 10 people (60%) reported this effect in the placebo group, leading to a non-significant difference between the two groups.

In the publication by Fallah, Shoroki, and Ferdosian (2015), which assessed, without a control group, the efficacy and safety of administering 0.3 mg/kg/d of melatonin for three months in the preventive treatment of migraine in children, 14 out of 60 children (23%) presented with daytime sleepiness, which resulted in three of them discontinuing treatment. The effects disappeared two or three weeks after stopping melatonin.

Many other publications dealing with the efficacy and safety of melatonin, administered over several days, weeks or months, have listed sleepiness as an adverse effect felt by the participants. The melatonin doses used in these tests were between 0.05 mg/d and 10 mg/d (Arendt 1997, Buscemi *et al.* 2005, Buscemi *et al.* 2006, EMA 2007, Miano *et al.* 2008, Hoebert *et al.* 2009, Gringras *et al.* 2012, Costello *et al.* 2014, Xu *et al.* 2015). In the majority of studies, either the occurrence of sleepiness was not significant compared to a placebo, or no data on the significance of the occurrence were available.

In order to objectively confirm this sleepiness, Cajochen *et al.* (1996) conducted two double-blind placebo-controlled experiments in eight healthy male students. In the first, 5 mg of melatonin was administered at 18:00. In the second, the single dose of 5 mg was administered at 13:00. Every 30 minutes, a self-assessment of fatigue and mood was conducted. In parallel, saliva was collected to analyse the melatonin content. Electroencephalograms (EEG) were also performed. In both experiments, the administration of melatonin significantly increased subjective sleepiness, compared to the placebo. The EEG results showed an increase in the theta/alpha frequencies of the EEG after the administration of melatonin, enabling the assessed sleepiness to be objectively confirmed. Lastly, the authors showed that the increase in the theta/alpha frequencies of the EEG appeared at the same time as the increase in concentrations of salivary melatonin, while the increase in subjective sleepiness occurred later. Exogenous melatonin therefore acts immediately on the EEG. The authors caution as to any possible impairment of vigilance after the administration of melatonin.

Based on this finding, Suhner, Schlagenhauf, Tschopp*, et al.* (1998) wanted to study the impact of melatonin administration on road driving performance. For this, 20 healthy men and women aged from 21 to 57 years were recruited for a randomised, placebo-controlled, double-blind crossover study. Each day of the test, 5 mg of melatonin or a placebo were administered at 16:30. An hour later, a series of tests were performed and subjective sleepiness was assessed. Selective attention was the only objective parameter significantly affected by melatonin with, however, values still within the normal range. Neither the clinical examination nor body sway were influenced by the administration of melatonin. Subjective sleepiness was increased by melatonin, although the result was only significant after a prolonged concentration task. Because subjective sleepiness increased after the administration of this hormone, the authors recommend that caution should be exercised when driving under the influence of melatonin.

The SPC for Circadin® states that "*Circadin® may cause drowsiness, therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety*" (Vidal 2017).

Despite the high frequency of occurrence of symptoms such as headaches, dizziness or discomfort and the presence of explanatory physiological data, it is difficult to conclude as to melatonin's role in the onset of these symptoms or a threshold dose for their occurrence. This is because most of the data come from efficacy studies, where the occurrence of these effects was not significant compared to the placebo. In other studies, the lack of a placebo group means that the onset of the effects cannot be objectively confirmed. In addition, the causality of melatonin in the occurrence of the effect is never studied. Lastly, the doses used in these different studies are mostly higher than that authorised in food supplements in France.

The occurrence of sleepiness following the administration of melatonin is explained by its hypnotic properties. While the cases of sleepiness were mostly reported for melatonin doses higher than those found in food supplements, people practising activities where a reduction in vigilance could have implications on their personal safety or that of others should not consume food supplements containing melatonin.

- **Digestive effects**

Two cases of abdominal pain and vomiting, where causality was deemed likely, were reported under the nutrivigilance scheme.

Gastrointestinal disorders are adverse effects frequently reported following the administration of melatonin (Claustrat 2009). Indeed, many cases have been observed in different studies where melatonin was administered for several days, weeks or months, at doses ranging from 0.1 mg/d to

10 mg/d (Suhner, Schlagenhauf, Johnson*, et al.* 1998, Buscemi *et al.* 2005, EMA 2007, Hoebert *et al.* 2009, Wade *et al.* 2010, Gringras *et al.* 2012, Wade *et al.* 2014, Costello *et al.* 2014, Fallah, Shoroki, and Ferdosian 2015). However, the occurrence of these effects was generally the same in the placebo group, when there was one. In addition, for studies where several doses were tested, no data were provided on the melatonin dose responsible for the adverse effect.

Studies have revealed the existence of melatonin receptors in the gastrointestinal tract. The activation of these receptors could explain certain digestive disorders observed, by an effect on intestinal motricity (Guardiola-Lemaître 1997).

The onset of gastrointestinal disorders is frequently reported after the administration of melatonin. The presence of receptors in the gastrointestinal tract could explain some of these effects. However, there are no data on the significance of their occurrence compared to control groups.

- **Cardiovascular effects**

Two cases of palpitations, where causality was deemed likely, were received under the nutrivigilance scheme. Two cases of tachycardia and bradycardia, where causality was deemed possible, were also reported in the context of suicide attempts.

One case of palpitations was reported in a study by Wade *et al.* (2010), funded by the pharmaceutical industry. A 68-year-old woman who had taken 2 mg/d of melatonin for several weeks experienced palpitations. This effect was considered to be probably linked to melatonin. This person had a history of palpitations.

In the study by Fallah, Shoroki, and Ferdosian (2015), designed to assess the efficacy and safety of 0.3 mg/kg/d of melatonin for three months in the preventive treatment of migraine in children, a moderate hypotension was observed in two children (4%). In the absence of a control group, the significance of the occurrence of this effect could not be assessed.

Four other studies showed that melatonin, at the single dose of 1 mg, could reduce blood pressure, vascular reactivity, the pulsatility index in the internal carotid artery and circulating catecholamines in healthy participants, compared to a placebo. Some of these effects can be explained by the presence of melatonin receptors (MT1 and MT2) in vascular and cardiac tissues (cardiomyocytes, left ventricle and coronary arteries). The activation of MT1 receptors leads to vasoconstriction whereas the activation of MT2 receptors leads to vasodilation. However, the vaso-regulatory actions of melatonin are complex and may involve both central and peripheral mechanisms. Moreover, lower melatonin concentrations than in healthy subjects have been identified in people suffering from conditions of cardiovascular origin such as high blood pressure, congestive heart failure and ischaemic heart disease, or after an acute myocardial infarction (Pandi-Perumal *et al.* 2017).

As part of the marketing authorisation (MA) application for Circadin®, the pharmaceutical laboratory Neurim analysed the cardiovascular parameters of 38 patients with disorders of this type. Two milligrams of melatonin per day for four weeks did not modify heart rate or blood pressure in these patients (EMA 2007).

The literature contains few reports of adverse cardiovascular effects following the consumption of melatonin. The adverse effects observed in the cases reported in nutrivigilance may be associated with the melatonin receptors found in the cardiovascular system. However, the products involved, sometimes consumed as part of a suicide attempt in combination with drugs, contained many other components that could explain the cardiovascular effects.

➢ **Neurological effects**

Three cases of neurological effects received under the nutrivigilance scheme were analysed. They involved one case of serotonin syndrome (agitation, hallucination, excessive perspiration) and two cases of tremors, one of which was accompanied by spasms. Their intrinsic causality was deemed to be likely.

These specific symptoms were not found in the literature; however, other adverse effects of a neurological nature have been documented.

- **Migraine**

Citera *et al.* (2000) conducted a study, without a placebo control, whose aim was to assess the effect of 3 mg of melatonin on sleep disorders, fatigue and pain in 21 patients with fibromyalgia. One woman left the study following the onset of migraine headaches after taking melatonin. A link between the consumption of melatonin and the onset of migraine was established due to the disappearance of symptoms after the cessation of treatment and their recurrence on its reintroduction.

Several studies have shown that plasma concentrations of endogenous melatonin or urinary concentrations of 6-sulphatoxymelatonin are lower in migraine sufferers (Claustrat *et al.* 1989, Masruha *et al.* 2010, Kozak *et al.* 2017).

The article by Annoni and Cook (2011) reports the case of a 37-year-old man who, for more than 15 years, had experienced four to six migraine attacks with aura yearly. In 2004, he began taking 3 to 6 mg of melatonin, two to four times per month, to help induce sleep. The frequency of his migraine attacks increased, and around eight times out of 10, morning attacks with aura were triggered 24 to 48 hours after taking melatonin. The intensity of the migraine seemed to be at least partly dose dependent. In December 2010, he stopped taking melatonin and had suffered no further attack by the time of his most recent medical visit in July 2011. The authors of this article suggest that the migraine attacks may be associated with a reduction in melatonin concentration caused by the withdrawal of exogenous melatonin intake. This case suggests that melatonin may play a role in the onset of migraine.

- **Epilepsy**

The available data indicate that melatonin concentrations in patients with intractable epilepsy were lower than those in controls (subjects not presenting with sleep disorders or neurological conditions). However, they increased threefold in the 24 hours after seizures (Bazil *et al.* 2000).

In a 1998 study, melatonin was administered to six children with neurological disabilities and chronic sleep disorders. The treatment consisted in administering 5 mg of melatonin by the oral route or *via* a gastrostomy tube at the patient's usual bedtime. In four of the treated patients (67%), a worsening or triggering of an epilepsy seizure was reported, leading to the study being stopped. The evolution of the seizures was systematically favourable after discontinuation of melatonin (Sheldon 1998).

In another study, a boy developed mild generalised epilepsy after receiving 5 mg/d of melatonin for four months (Smits *et al.* 2001).

Lastly, Sandyk, Tsagas, and Anninos (1992) published the case of a 21-year-old woman suffering from uncontrolled epilepsy, whose epileptiform activity was measured by magnetoencephalography (MEG) 45 minutes after being administered 3 mg of melatonin. The results indicated an increase in epileptiform activity and the patient reported having experienced four brief seizures in the afternoon, each lasting a few seconds.

Inversely, some articles show an anticonvulsant property of melatonin, proposed as resulting from it increasing brain GABA concentrations. Jain and Besag (2013) conducted a literature review on the existing data on the role of exogenous melatonin in epilepsy. In 26 articles published between

January 1990 and May 2012 that reported an association between melatonin and epilepsy, seven did not provide relevant information. Two randomised, double-blind, controlled trials showed no effect of melatonin on the incidence of epilepsy seizures. Seven studies, including one double-blind, placebo-controlled trial, revealed a reduction in the frequency of seizures. The open studies reported conflicting results. The authors stressed the lack of available data, the small number of studies and the need to conduct randomised, double-blind, placebo-controlled trials on this subject. They indicated, however, that it is reasonable to conclude provisionally that melatonin has no marked effect on epilepsy seizures.

- **Restless legs syndrome**

One study suggested that melatonin, by inhibiting dopamine transmission, could aggravate the symptoms associated with restless legs syndrome. Whittom *et al.* (2010) administered 3 mg of melatonin at 19:00 to eight subjects suffering from primary restless legs syndrome, in order to study the impact of the increase in circulating concentrations of exogenous melatonin on motor symptoms. These symptoms were aggravated in all subjects receiving the exogenous melatonin. The authors reiterated, however, that the main limitation to this study was the small number of people included.

The onset of migraine and the aggravation of restless legs syndrome following consumption of melatonin cannot be ruled out.

The influence of melatonin on the triggering of epileptic seizures, whether in patients whose seizures were controlled or not controlled by treatment, is controversial and still insufficiently documented. In this context of uncertainty, people suffering from epilepsy should not consume food supplements containing melatonin without seeking the advice of their doctor.

➢ **Psychiatric effects**

Only one case of a psychiatric effect was analysed under the nutrivigilance scheme. It was a case of nightmares, where causality was likely. Other adverse effects of a psychiatric nature were identified during the analysis of the literature (agitation, mood disorders, depression).

- **Nightmares**

The case of the occurrence of nightmares reported to the nutrivigilance scheme concerned an 87-year-old man who, in order to withdraw from a hypnotic agent (Zopiclone), consumed two capsules of a food supplement containing 1 mg of melatonin. He fell asleep without difficulty but woke up after 4 hours of nightmares. The next day, he stopped taking the melatonin and resumed the Zopiclone.

Nightmares occurring after taking melatonin are among the effects frequently reported in the literature (Guardiola-Lemaître 1997). This effect was reported, for example, for a dose of 3 mg/d for 4 months in postmenopausal women (Chen *et al.* 2014) or in children after a regular dose (from 2-3 times per week to several times per year) of 0.5 mg/d to 10 mg/d of melatonin for 1 to 57 months (Hoebert *et al.* 2009).

In the study by Jockovich *et al.* (2000), 1 mg/d of melatonin was administered for three days to 19 healthy subjects. No adverse effects were reported except for abnormal dreams in one subject who, moreover, reported an increase in psychosocial stress factors at the time of the experiment due to personal circumstances independent of the study.

One case of onset of nightmares following the consumption of 8 mg of ramelteon, a melatonin receptor agonist, has also been published. The frequency of nightmares decreased after this product was discontinued (Shah and Kablinger 2015).

- **Agitation/mood**

Mood disorders or agitation have been reported in individuals with behavioural or psychiatric disorders.

Riemersma-van der Lek *et al.* (2008) conducted a randomised, double-blind placebo-controlled trial to determine the individual or combined impact of bright light and melatonin (2.5 mg/d for an average duration of 15 months) on cognitive decline, mood, behaviour and sleep disturbances in 189 elderly people, 87% of whom have dementia. The results show that melatonin alone negatively affected the mood of participants according to the observations of the caregivers. The authors of this article concluded that the long-term use of melatonin by the elderly can only be recommended in combination with light, to counteract its adverse effects on mood.

Gringras *et al.* (2012) conducted a randomised, double-masked, placebo-controlled study whose aim was to assess the effectiveness and safety of melatonin administered for 12 weeks in the treatment of severe sleep problems in children (146 children aged 3 to 15 years) with neurodevelopmental disorders. The children in the treated group started with a melatonin dose of 0.5 mg/d, which was then increased to 2, 6 or 12 mg/d according to their response to the treatment. Sixteen out of the 70 children in the group treated by melatonin (23%) reported changes in mood, *versus* 17 out of 76 in the placebo group (22%). Thirteen children (19%) presented with increased excitability in the treated group, compared with 16 (21%) in the placebo group. No formal statistical tests were conducted to assess the significance of these effects.

Richings and Feroz-Nainar (2010) described three cases of patients with an intellectual disability treated by various psychotropic drugs, in whom treatment with melatonin was associated with an increase in agitation. The daily doses involved were 2.5 mg, 6 mg and 10 mg. In each case, the effects lessened after discontinuation or a decrease in the dose of melatonin. The authors suggest that melatonin should be used with caution in people with an intellectual disability or mental disorders, especially those with a history of agitation.

Braam *et al.* (2008) conducted a randomised placebo-controlled study on 51 children with chronic sleep disorders related to an intellectual disability. For 4 weeks, individuals aged 6 years or over received either 5 mg of melatonin in a quick-release tablet or a placebo every day at 19:00. Individuals under 6 years of age received a daily dose of 2.5 mg of melatonin at 18:00. In the treated group, five out of 29 individuals (17%) presented with increased crying during the day and agitation. These effects were not observed in the placebo group.

- **Depression**

Lastly, a few data are available on the effect of melatonin on people suffering from depression.

Carman *et al.* (1976) conducted a study on six patients with major primary depression and two patients with Huntington disease. They received varying doses of melatonin either orally, divided into four equal daily doses, or intravenously, once or twice a day for 3 to 12 days. The oral doses could go up to 1600 mg/d. The intravenously-administered dose could go up to 250 mg/d. This study showed an exacerbation of the depression, and the study was discontinued in view of melatonin's negative role in the depression of the patients included in the study. The doses used in this study were far higher than those typically found in the literature.

Force, Hansen, and Bedell (1997) reported a case of acute psychosis occurring in a person who appeared to have consumed a high dose of melatonin (around 30 mg) in combination with fluoxetine (10 mg). This was a 73-year-old woman with a history of depression and anxiety, but not psychosis, who every day consumed 10 mg of fluoxetine, 3 to 6 mg of melatonin, conjugated oestrogens for osteoporosis prevention (1.25 mg/d) and vitamins, as well as a beclometasone nasal spray in the event of allergic rhinitis. Admitted to the hospital for a confusional state, delusions and paranoia, she reported at the time that she had taken 10 tablets of melatonin on that very morning. After a night in hospital, her mental state returned to normal. She then stated that she had not taken more than 1 or 2 tablets of melatonin. The authors of the case study suggested

that the patient's psychotic episode was the consequence of a possible interaction between melatonin and fluoxetine.

Nightmares, altered mood or agitation and an exacerbation of depression have been reported after the consumption of melatonin. Melatonin has a mood modulation effect. The available data concern specific populations, suffering from behaviour or mood disorders and with doses higher than those found in food supplements.

People with mood, behaviour or personality disorders should not consume food supplements containing melatonin without seeking the advice of their doctor.

- **Dermatological and allergic effects**

One single analysable case of a dermatological effect was received under the nutrivigilance scheme. It relates to a case of pruritus and blotches appearing on the body and the scalp, where causality was possible. Concerning allergic effects, one case of anaphylactic shock, where causality was possible, was reported under the nutrivigilance scheme.

These types of effects are very rarely reported in the literature. One article described the appearance of two independent cases of penile eruption in men aged 35 and 42 years who had consumed the same product containing 3 mg of melatonin. The first patient indicated that he took it each time he travelled abroad and had experienced a similar episode four months earlier. The second patient's history is not known. In both patients, an oral challenge test was carried out, consisting in the administration of 1 mg of pure melatonin. Six to eight hours later, blotches emerged in both patients on the previously affected sites, accompanied by a burning sensation. The lesions disappeared over the next 10 days, without any sequelae (Bardazzi *et al.* 1998).

The other available data concern cases of adverse effects reported in studies of the effectiveness of melatonin. Hoebert *et al.* (2009), in their study on the long-term (1 to 57 months) effectiveness and safety of 0.5 to 10 mg/d of melatonin in children with attention-deficit disorder and chronic sleep-onset insomnia, observed a change in skin pigmentation in two children (2%). Another study, whose objective was to observe the long-term effects of oral administration of melatonin on human skin colour, did not show any modification of pigmentation in seven patients with malignant melanoma following consumption of melatonin (5 to 700 mg/m^2/d) for 5 to 32 months (McElhinney *et al.* 1994).

The study by Gringras *et al.* (2012), described above, assessing the effectiveness and safety of melatonin in the treatment of severe sleep problems in 146 children with neurodevelopmental disorders, reported 11 cases (16%) of skin rash in the group treated with 2, 6 or 12 mg/d of melatonin for 12 weeks, compared with 8 cases (11%) in the placebo group. No statistical tests were conducted to assess the significance of this effect.

In a randomised, double-blind, placebo-controlled study conducted in 72 children suffering from chronic sleep disorders, receiving 0.05, 0.1 or 0.15 mg/kg/d of melatonin or a placebo for a week, 15 children (21%) presented with redness in the cheeks, ears and eyes within an hour of administration. The redness in the cheeks was reported in the three melatonin dose groups with a higher frequency for the group receiving the highest dose (Van Geijlswijk *et al.* 2010).

Lastly, no cases of allergy to melatonin have been reported to the Allergo-Vigilance network[27].

Few cases of adverse dermatological effects following the consumption of melatonin have been reported in the literature.

[27] The Allergo-Vigilance network was created in 2001. Its main mission is to keep a register of severe anaphylaxis cases.

No allergy cases have been reported in the literature, with the exception of one case in nutrivigilance for which no allergy test results are available.

- **Uro-nephrological effects**

A single case of adverse uro-nephrological effects, where causality was considered to be doubtful, was received under the nutrivigilance scheme. It reported the onset of immuno-allergic tubulointerstitial nephritis in a woman suffering from ankylosing spondylitis.

The only uro-nephrological effects reported in the literature concern the effects of melatonin on urination or cases of nocturnal incontinence. Van Geijlswijk *et al.* (2010) conducted a randomised double-blind placebo-controlled study of 72 children aged 6 to 12 years, with chronic sleep disorders. For one week, they received 0.05, 0.1 or 0.15 mg/kg/d of melatonin or a placebo. One participant, receiving a dose of 0.05 mg/kg/d of melatonin, discontinued treatment due to night incontinence that the mother attributed to the product. Two other participants, who received a dose of 0.1 and 0.15 mg/kg/d of melatonin, reported an increase in urination in the evening and at night.

Other cases of night incontinence occurred after long-term administration of 0.5 mg to 10 mg/d of melatonin to children with attention-deficit disorder and chronic sleep-onset insomnia (Hoebert *et al.* 2009).

No other cases of uro-nephrological effects and no data on the potential nephrotoxicity of melatonin were found in the literature.

Very few data are available on the urological and nephrological effects of melatonin. The only observed effects were incontinence or increased urination at night in children.

- **Hepatic effects**

One case of hepatic cytolysis, where causality was possible, was received under the nutrivigilance scheme. It concerned a woman who had been diagnosed with autoimmune hepatitis. This case will be described in the next section relating to the effects of melatonin on the immune system.

The only data available in the literature on the hepatotoxicity of melatonin concern the description of hepatitis cases involving an autoimmune mechanism.

- **Effects on inflammatory or autoimmune diseases**

Melatonin is known to have immunomodulatory properties. It regulates the immune system by exerting its action at different levels, through the stimulation of its receptors found on the immunocompetent cells, the maintenance of cell proliferation and the modulation of cytokine production (Rivara *et al.* 2015).

As indicated previously, one case of immuno-allergic tubulointerstitial nephritis occurring in a woman with ankylosing spondylitis was analysed in nutrivigilance. Causality was determined to be doubtful because of the concomitant use of NSAIDs, known for their potential to cause this type of adverse effect.

One case of hepatic cytolysis received under the nutrivigilance scheme and found to have possible causality concerned a 60-year-old woman with autoimmune hepatitis. Immunosuppressive treatment had been discontinued in 2014. In September 2015, she had started consuming a food supplement containing melatonin. A few days later, there was a sudden onset of asthenia. The test results revealed acute cytolytic hepatitis. She presented with an associated cholestatic syndrome. The clinical examination showed no hepatosplenomegaly, peripheral lymphadenopathy or other

signs of hepatocellular failure. Serological tests for hepatitis A, B and C, EBV and HHV-6 were negative. Anti-smooth muscle, anti-mitochondria and anti-LKM1 antibodies were negative. Anti-nuclear antibodies were positive at 1/160th. The members of the Working Group concluded that the triggering of a new autoimmune hepatitis attack by the food supplement could not be excluded.

One case of autoimmune hepatitis occurring after consumption of melatonin was published by Hong and Riegler (1997). It concerned a 39-year-old woman with no prior medical history, who had consumed 3 mg/d of melatonin for two weeks for insomnia. A week after discontinuation, she complained of emotional irritability and fatigue. After the onset of jaundice, she went to the hospital, where she was diagnosed with autoimmune hepatitis. The authors indicated that the time between the taking of the melatonin and the development of the autoimmune hepatitis, as well as the immunomodulatory properties described for this compound, suggest a possible role of melatonin in the development of this autoimmune disorder. They put forward the hypothesis of stimulation by melatonin of T lymphocyte activity, which can lead to the production of auto-antibodies that may cause autoimmune hepatitis in some individuals.

Lastly, Fourman and Robert Meyer (2013) reported the development of autoimmune hepatitis in a 50-year-old man, one month after starting consumption of 8 mg of ramelteon (a melatonin receptor agonist). With regard to the compatibility of the condition's onset time after taking the ramelteon with the immunostimulatory activities of the melatonergic compounds, they conclude that this product played a role in the development of the autoimmune hepatitis in this patient.

In addition, Calvo *et al.* (2002) described the case of a woman suffering from Crohn's disease and treated with corticosteroids and sulfasalazine. In April 2000, the patient decided to take 3 mg capsules of melatonin before bedtime. Four days later, she began to feel the symptoms of the active phase of Crohn's disease (diarrhoea, abdominal cramps). Twenty-four hours after discontinuing melatonin, there was a complete remission of symptoms. The authors concluded that in Crohn's disease and probably in other immune dysfunction diseases, the secretion of various cytokines (IL-2 and IL-12) induced by melatonin may exacerbate the symptoms of these diseases.

The same team also published the case of a 56-year-old man suffering from ulcerative colitis treated by corticosteroids and sulfasalazine, who presented with the symptoms of the active phase of his disorder two months after beginning consumption of 3 mg/d of melatonin. Initially, the melatonin was continued and the corticosteroid doses increased. Because the symptoms had not ceased, the patient was hospitalised and the melatonin treatment was discontinued. Twenty-four to 48 hours later, the patient was in full remission (Maldonado and Calvo 2008).

Lastly, serum concentrations of endogenous melatonin are higher in patients with rheumatoid arthritis than in healthy subjects (Sulli *et al.* 2002). In addition, several studies conducted on animal models suggest that melatonin tends to promote the development of rheumatoid arthritis or an increase in its severity (Lin *et al.* 2013).

Several cases of onset or reactivation of inflammatory diseases (Crohn's disease, ulcerative colitis and rheumatoid arthritis) and auto-immune diseases (hepatitis) after the consumption of melatonin have been described in the literature. The consumption of food supplements containing melatonin should be avoided in people suffering from inflammatory or autoimmune diseases.

- **Effects on the respiratory system**

Some reports of adverse respiratory effects were received under the nutrivigilance scheme. They could not be analysed as they were insufficiently documented. However, data were found in the literature on this type of effect and are presented below.

Teams have worked on the role of melatonin in the pathogenesis of asthma. Sutherland *et al.* (2002) showed that melatonin, at physiological doses, was proinflammatory and associated with an increase in the production of TNFα and interleukin 1 and 6 proinflammatory cytokines in five

healthy volunteers or 18 asthmatics (particularly for those with nocturnal asthma). In 2003, the same team found significantly higher concentrations of endogenous melatonin in seven people with nocturnal asthma than in 11 healthy people (67.6 ± 5.0 pg/mL compared with 53.5 ± 4.0 pg/mL). It also found a delay in melatonin secretion in asthmatics (Sutherland *et al.* 2003). Another study that assessed *in vitro* the role of melatonin in tracheal ring muscle tone in rats showed that treatment by melatonin strengthened the contraction responses, but did not affect the relaxation responses (Karasu-Minareci, Kaya, and Yildirim 2012). All of these authors concluded that there was a potential adverse effect of melatonin in asthma and recommended that people with asthma avoid its consumption.

These data should be compared with other studies highlighting the anti-inflammatory nature of melatonin and its potential beneficial role in asthma or other respiratory diseases (Nabavi *et al.* 2017). Lastly, in a randomised double-blind placebo-controlled study, Campos *et al.* (2004) showed that the administration of 3 mg/d of melatonin for four weeks improved sleep in 12 people with asthma, without any sign of worsening respiratory symptoms.

The data on the role of melatonin in the triggering of asthma attacks are contradictory. In this context of uncertainty, asthmatics should not consume food supplements containing melatonin without seeking the advice of their doctor.

- **Effects on glucose and insulin metabolism**

No sufficiently documented cases of nutrivigilance relating to endocrine effects could be analysed, but data are found in the literature.

In a single-blind placebo-controlled study including 21 healthy women, Rubio-Sastre *et al.* (2014) observed a decrease in tolerance during glucose tolerance tests after administration of 5 mg of melatonin. Effects on insulin secretion (for the tests carried out in the morning) and on the sensitivity to it (evening) were identified. The authors concluded as to a possible interaction between melatonin and glucose tolerance, particularly in subjects predisposed to a glucose intolerance, and suggested that melatonin should not be taken at mealtimes.

Melatonin plays an important role in the regulation of glucose metabolism and blood insulin levels but the exact mechanism of its actions has not been established. It has been suggested that melatonin may act directly on the hepatocytes and pancreatic β-cells. In addition, studies have shown that diabetic patients had lower nocturnal melatonin concentrations than those of non-diabetics (Lardone *et al.* 2014).

Two long-term studies (5 and 6 months) were conducted by the Neurim laboratory, as part of the marketing authorisation application for Circadin®, including a total of 80 people with type 2 diabetes and suffering from insomnia. No deleterious influence on glycaemic control was found for this population at a dose of 2 mg/d (EMA 2007).

Melatonin is involved in the regulation of blood insulin levels and glucose metabolism, but no particular risk to diabetics can be inferred from the data in the literature.

- **Other effects**

Two cases of rheumatologic disorders were reported to the nutrivigilance scheme: a case of myalgia and a case of arthralgia associated with cramps, where causality was considered likely.

One case of otorhinolaryngologic disorders was also reported. It was a case of burning mouth and redness in the throat, where causality was considered likely.

In the study by Wade *et al.* (2010), funded by the Neurim laboratory, nasopharyngitis and arthralgia were the most frequently reported adverse effects, both in the group treated with 2 mg of prolonged-release melatonin for several weeks and in the placebo group. The authors concluded that the safety profile of melatonin was similar to that of the placebo regarding the incidence and type of adverse effects reported.

Cases of rheumatologic or otorhinolaryngologic disorders have only been reported in nutrivigilance. To date, there are no data in the literature implicating melatonin in the occurrence of these types of effects.

3.2.6. Drug interactions

In the absence of specific data on the interactions of food supplements containing melatonin, the data considered here are mainly those derived from the SPC for Circadin® (Vidal 2017).

- **Pharmacokinetic interactions**

Pharmacokinetic interactions can occur between melatonin and co-administered medicinal products. The isoenzymes CYP1A1, CYP1A2 and CYP1B1 or CYP2C19 are involved in the metabolism of melatonin (Ma *et al.* 2005, Vidal 2017). Interactions are therefore possible between melatonin and other active substances that induce or inhibit these enzymes and/or are metabolised by them. In patients treated with 5- or 8-methoxypsoralen, cimetidine or quinolones, or on oestrogen therapy (e.g. contraceptives or hormone replacement therapy), an increase in plasma concentrations of melatonin may be observed as a result of a decrease in its metabolism.

Fluvoxamine inhibits CYP1A2, but also the re-uptake of serotonin, a precursor of melatonin. An increase in the plasma concentration of melatonin administered with fluvoxamine has been observed.

The *in vitro* induction of CYP3A by melatonin has also been shown. Although the clinical relevance of this induction is not known, a decrease in the plasma concentration of medicinal products metabolised by this isoform in the event of co-administration with melatonin is possible.

Given the strong binding of melatonin to albumin, α1-acid glycoprotein and high-density lipoprotein, interactions with drugs binding to the same plasma macromolecules may occur.

- **Pharmacodynamic interactions**

Pharmacodynamic drug interactions have also been described. Melatonin may amplify the sedative properties of benzodiazepines and other hypnotics, such as zolpidem, zopiclone or zaleplon (not marketed in France). One clinical trial showed that the concomitant administration of melatonin and zolpidem resulted in increased impairment of attention, memory and coordination, compared to zolpidem used alone. Similarly, studies have shown that melatonin, when administered concomitantly with imipramine and thioridazine (not marketed in France), increased the difficulty in performing tasks, compared to imipramine used alone, and caused more pronounced dizziness compared to thioridazine used alone (Vidal 2017).

Lusardi, Piazza, and Fogari (2000) showed that the concomitant use of melatonin with nifedipine reduced the latter's antihypertensive effect and could lead to a loss of control of hypertension. However, it is also possible that melatonin may potentiate the effects of antihypertensive drugs (Sajith and Clarke 2007). These effects could be related to melatonin's effects on vasomotricity.

Melatonin has an inhibitory effect on platelet aggregation, and may potentiate the effects of other platelet inhibitors such as aspirin or anticoagulants such as warfarin. In addition, the

immunomodulatory effects of melatonin could counteract the effects of anti-inflammatory agents such as corticosteroids (Sajith and Clarke 2007).

Melatonin may modify the plasma concentration of drugs metabolised by the isoenzymes CYP1A1, CYP1A2 and CYP1B1 or CYP2C19.

A pharmacodynamic interaction is possible between melatonin and platelet inhibitors, anticoagulants, anti-inflammatory agents and substances acting on the central nervous system, particularly hypnotic and antiepileptic agents.

In general, the consumption of food supplements containing melatonin in combination with drug therapy should be discussed with a doctor or pharmacist.

3.3. Vulnerable populations and at-risk situations

3.3.1. Pregnancy and breast-feeding

It has been demonstrated that endogenous melatonin plays an essential role during pregnancy and in foetal development, especially in the brain. For this, melatonin is proposed as a possible treatment for certain conditions in pregnancy (pre-eclampsia, threat of premature birth, intrauterine growth restriction) and brain damage in the perinatal period. Clinical studies are currently in progress (Sagrillo-Fagundes *et al.* 2016). However, no data are available on the effect of melatonin administration to pregnant women with a normal pregnancy.

Endogenously-produced melatonin has been detected in breast milk (Illnerová, Burešová, and Presl 1993, Vidal 2017). This observation suggests that melatonin from an exogenous source could pass into breast milk (Vidal 2017). Amer *et al.* (2015) believe that the melatonin concentration in breast milk could increase from 0.4 to 1 µg/L for 1 mg of exogenous melatonin consumed by the mother. They conclude that long-term consumption of this substance could alter the natural development of the child's circadian rhythm and their sleep cycle.

In light of the results of reprotoxicity studies conducted in animals and in the absence of clinical data, the consumption of food supplements containing melatonin is not recommended in pregnant women.

Because exogenous melatonin passes into breast milk, breastfeeding women should not consume it in the form of a food supplement.

3.3.2. Children and adolescents

Data are available in the literature on the effectiveness and safety of melatonin in the treatment of sleep disorders in children and adolescents with mental and neurological disorders, autism, etc. (Sánchez-Barceló, Mediavilla, and Reiter 2011). In addition, in France, Circadin® benefits from an RTU for children over 6 years of age, for disturbances of the sleep-wake cycle related to developmental disorders and neurogenetic diseases. This treatment is subject to a strict monitoring protocol.

For healthy children and adolescents, the safety data are insufficient. Kennaway (2015) indicated that because of its effects on other hormones, melatonin may interfere with development during adolescence. He also stated that the endocrine effects of the long-term administration of melatonin in children and adolescents are unknown.

In the absence of sufficient safety data, the consumption of food supplements containing melatonin by children and adolescents is not recommended.

3.3.3. Other populations

Other sensitive populations or risk situations were identified following the analysis of the literature and nutrivigilance cases. This information is presented in Sections 3.2.5.2 and 3.2.6.

People with epilepsy, asthma, or suffering from mood, behaviour or personality disorders should not consume food supplements containing melatonin without seeking the advice of their doctor.

People suffering from inflammatory or autoimmune diseases should not consume melatonin in the form of a food supplement.

The consumption of food supplements containing melatonin in combination with drug therapy should be discussed with a doctor or pharmacist.

Melatonin should not be consumed before any activity requiring sustained vigilance and posing a possible safety problem in case of drowsiness.

3.4. Conclusions and recommendations of the CES and the WG

Melatonin is a hormone whose main physiological function is to provide the body with information on the nychthemeron, thus promoting sleep. In France, it is available on the market in the form of a medicinal product (Circadin®), extemporaneous preparation or food supplement.

Ninety cases of adverse effects occurring following the intake of food supplements containing melatonin have been brought to the attention of the nutrivigilance scheme. Other reports have been received by the toxicovigilance schemes and vigilance systems of a few Member States of the European Union and of Canada. The adverse effects reported are very diverse, primarily general symptoms and neurological, digestive and psychological disorders. The melatonin dose consumed is not always known.

Toxicological, mechanistic and clinical data on melatonin, confirmed by some of the nutrivigilance cases, have helped identify sensitive populations, leading the CES to:

- advise against the consumption of melatonin in the form of food supplements by:
  - people suffering from inflammatory or autoimmune diseases;
  - pregnant or breastfeeding women;
  - children and adolescents;
  - people carrying out any activity requiring sustained vigilance and posing a possible safety problem in case of drowsiness.
- recommend seeking medical advice regarding the consumption of melatonin in the form of food supplements for:
  - people with epilepsy;
  - asthmatics;
  - people with mood, behaviour or personality disorders.

Pharmacokinetic interactions have been identified between melatonin and drugs metabolised by the isoenzymes CYP1A1, 1A2 and 1B1 or 2C19. Pharmacodynamic interactions with melatonin are also possible, especially for substances acting on the central nervous system and hypnotics in particular.

The CES recommends that the consumption of food supplements containing melatonin in combination with drug therapy should be discussed with a doctor or pharmacist.

In the absence of sufficient data on the long-term effects of melatonin consumption, the CES recommends limiting the consumption of these food supplements to occasional use.

Because certain risks have been identified for high doses, the CES recommends that consumers do not exceed a dose of 2 mg per day of melatonin.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the recommendations of the Working Group on "Nutrivigilance" and the Expert Committee on “Human Nutrition”.

ANSES conducted an analysis of the 90 reports of adverse effects likely to be associated with the consumption of food supplements containing melatonin, received between the creation of the nutrivigilance scheme in 2009 and May 2017. This analysis was supplemented by the study of bibliographic data, enabling ANSES to identify the risks associated with their use.

The expert appraisal highlighted the existence of populations and situations at risk. In particular, these include breastfed children whose mothers may have consumed food supplements containing melatonin, children and adolescents, people suffering from inflammatory or autoimmune diseases, people carrying out any activity requiring sustained vigilance where drowsiness could pose a safety problem, and people with epilepsy, asthma, or suffering from mood, behaviour or personality disorders.

Because of the many possible pharmacokinetic and pharmacodynamic interactions between melatonin and certain drugs, ANSES recommends, in the event of drug therapy, avoiding the use of food supplements containing melatonin without first seeking the advice of a doctor.

ANSES recommends favouring simple formulations that do not combine melatonin with other ingredients and avoiding the concomitant use of several food supplements, in order to limit the risks of interactions.

Consultations with the European focal points of the European Food Safety Authority (EFSA) revealed the wide variability in the regulatory status of melatonin in the European Union. In some countries, including Denmark and the Czech Republic, melatonin is prohibited in food supplements. In Belgium and in Germany, products providing 0.3 mg or more of melatonin per day are considered medicinal products by function, in light of their pharmacological activity. In Spain and Italy, melatonin is authorised in food supplements up to 1 mg per day. In France and Latvia in particular, the regulations authorise the marketing of food supplements providing less than 2 mg of melatonin per day. Considering that there are few data available on the safety of such doses and that a pharmacological activity cannot be excluded, ANSES believes it necessary for a harmonised regulatory framework to be defined at European level on the basis of safety studies conducted for doses below 2 mg.

In general, ANSES recommends that consumers:

- seek the opinion of a doctor whenever they have questions about the usefulness and safety of the consumption of food supplements;
- inform their doctor or pharmacist that they are taking food supplements.

ANSES reminds healthcare professionals of the need to report to its nutrivigilance scheme any adverse effects likely to be associated with the consumption of food supplements about which they become aware.

Lastly, ANSES emphasises the value of setting up a joint international project on the monitoring of adverse effects associated with the consumption of food supplements.

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KEYWORDS

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Nutrivigilance, adverse effects, food supplements, melatonin

REFERENCES

Acuña-Castroviejo, D., G. Escames, C. Venegas, M. E. Díaz-Casado, E. Lima-Cabello, L. C. López, S. Rosales-Corral, D. X. Tan, and R. J. Reiter. 2014. "Extrapineal melatonin: Sources, regulation, and potential functions." *Cellular and Molecular Life Sciences* 71 (16):2997-3025. doi: 10.1007/s00018-014-1579-2.

Amer, M. R., G. C. Cipriano, J. V. Venci, and M. A. Gandhi. 2015. "Safety of popular herbal supplements in lactating women." *Journal of Human Lactation* 31 (3):348-353. doi: 10.1177/0890334415580580.

Annoni, J. M., and S. Cook. 2011. "Migraine induced by melatonin withdrawal: A clue for future trials?" *Schweizer Archiv fur Neurologie und Psychiatrie* 162 (7):293-294.

ANSES. 2011. "Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à la construction d'une méthode d'imputabilité des signalements d'effets indésirables de nutrivigilance. (saisine 2010-SA-0195)." Maisons-Alfort, Fr: ANSES, 8 p.

ANSES. 2016. "Evaluation des risques sanitaires liés au travail de nuit." Maisons-Alfort, Fr: ANSES.

Arendt, J. 1997. "Safety of Melatonin in Long-Term Use(?)." *Journal of Biological Rhythms* 12 (6):673-681.

Bardazzi, F., F. Placucci, I. Neri, A. D'Antuono, and A. Patrizi. 1998. "Fixed drug eruption due to melatonin [3]." *Acta Dermato-Venereologica* 78 (1):69-70. doi: 10.1080/00015559850135913.

Bartoli, A. N., S. De Gregori, M. Molinaro, M. Broglia, C. Tinelli, and R. Imberti. 2012. "Bioavailability of a new oral spray melatonin emulsion compared with a standard oral formulation in healthy volunteers." *Journal of Bioequivalence and Bioavailability* 4 (7):96-99. doi: 10.4172/jbb.1000120.

Bazil, C. W., D. Short, D. Crispin, and W. Zheng. 2000. "Patients with intractable epilepsy have low melatonin, which increases following seizures." *Neurology* 55 (11):1746-1748.

Braam, W., R. Didden, M. Smits, and L. Curfs. 2008. "Melatonin treatment in individuals with intellectual disability and chronic insomnia: A randomized placebo-controlled study." *Journal of Intellectual Disability Research* 52 (3):256-264. doi: 10.1111/j.1365-2788.2007.01016.x.

Buscemi, N., B. Vandermeer, N. Hooton, R. Pandya, L. Tjosvold, L. Hartling, G. Baker, T. P. Klassen, and S. Vohra. 2005. "The efficacy and safety of exogenous melatonin for primary sleep disorders: A meta-analysis." *Journal of General Internal Medicine* 20 (12):1151-1158. doi: 10.1111/j.1525-1497.2005.0243.x.

Buscemi, N., B. Vandermeer, N. Hooton, R. Pandya, L. Tjosvold, L. Hartling, S. Vohra, T. P. Klassen, and G. Baker. 2006. "Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: Meta-analysis." *British Medical Journal* 332 (7538):385-388. doi: 10.1136/bmj.38731.532766.F6.

Cajochen, C., K. Kräuchi, M. A. Von Arx, D. Möri, P. Graw, and A. Wirz-Justice. 1996. "Daytime melatonin administration enhances sleepiness and theta/alpha activity in the waking EEG." *Neuroscience Letters* 207 (3):209-213. doi: 10.1016/0304-3940(96)12517-9.

Calvo, J. R., J. M. Guerrero, C. Osuna, P. Molinero, and A. Carrillo-Vico. 2002. "Melatonin triggers Crohn's disease symptoms [2]." *J Pineal Res* 32 (4):277-278. doi: 10.1034/k.1600-079X.2002.01881.x.

Campos, F. L., F. P. Da Silva-Júnior, V. M. S. De Bruin, and P. F. C. De Bruin. 2004. "Melatonin improves sleep in asthma: A randomized, double-blind, placebo-controlled study." *American Journal of Respiratory and Critical Care Medicine* 170 (9):947-951. doi: 10.1164/rccm.200404-488OC.

Cardinali, D. P., H. J. Lynch, and R. J. Wurtman. 1972. "Binding of melatonin to human and rat plasma proteins." *Endocrinology* 91 (5):1213-1218. doi: 10.1210/endo-91-5-1213.

Carman, J. S., R. M. Post, R. Buswell, and F. K. Goodwin. 1976. "Negative effects of melatonin on depression." *American Journal of Psychiatry* 133 (10):1181-1186.

Chen, W. Y., A. Giobbie-Hurder, K. Gantman, J. Savoie, R. Scheib, L. M. Parker, and E. S. Schernhammer. 2014. "A randomized, placebo-controlled trial of melatonin on breast cancer survivors: Impact on sleep, mood, and hot flashes." *Breast Cancer Research and Treatment* 145 (2):381-388. doi: 10.1007/s10549-014-2944-4.

Cipolla-Neto, J., F. G. Amaral, S. C. Afeche, D. X. Tan, and R. J. Reiter. 2014. "Melatonin, energy metabolism, and obesity: A review." *J Pineal Res* 56 (4):371-381. doi: 10.1111/jpi.12137.

Citera, G., M. A. Arias, J. A. Maldonado-Cocco, M. A. Lázaro, M. G. Rosemffet, L. I. Brusco, E. J. Scheines, and D. P. Cardinalli. 2000. "The effect of melatonin in patients with fibromyalgia: A pilot study." *Clinical Rheumatology* 19 (1):9-13. doi: 10.1007/s100670050003.

Claustrat, B. 2009. "Melatonin and sleep-wake rhythm disturbances." *Medecine du Sommeil* 6 (1):12-24. doi: 10.1016/j.msom.2009.02.001.

Claustrat, B., J. Brun, and G. Chazot. 2005. "The basic physiology and pathophysiology of melatonin." *Sleep Medicine Reviews* 9 (1):11-24. doi: 10.1016/j.smrv.2004.08.001.

Claustrat, B., C. Loisy, J. Brun, S. Beorchia, J. L. Arnaud, and G. Chazot. 1989. "Nocturnal Plasma Melatonin Levels in Migraine: A Preliminary Report." *Headache: The Journal of Head and Face Pain* 29 (4):242-245. doi: 10.1111/j.1526-4610.1989.hed22904242.x.

Comai, S., and G. Gobbi. 2014. "Unveiling the role of melatonin MT2 receptors in sleep, anxiety and other neuropsychiatric diseases: A novel target in psychopharmacology." *Journal of Psychiatry and Neuroscience* 39 (1):6-21. doi: 10.1503/jpn.130009.

Costello, Rebecca B., Cynthia V. Lentino, Courtney C. Boyd, Meghan L. O'Connell, Cindy C. Crawford, Meredith L. Sprengel, and Patricia A. Deuster. 2014. "The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature." *Nutrition Journal*. doi: 10.1186/1475-2891-13-106.

Dubocovich, M. L., P. Delagrange, D. N. Krause, D. Sugden, D. P. Cardinali, and J. Olcese. 2010. "International union of basic and clinical pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors." *Pharmacological Reviews* 62 (3):343-380. doi: 10.1124/pr.110.002832.

Ekmekcioglu, C. 2006. "Melatonin receptors in humans: Biological role and clinical relevance." *Biomedicine and Pharmacotherapy* 60 (3):97-108. doi: 10.1016/j.biopha.2006.01.002.

EMA. 2007. "Assessment report for CIRCADIN." ; Contract No.: EMEA/H/C/695.

Emet, M., H. Ozcan, L. Ozel, M. Yayla, Z. Halici, and A. Hacimuftuoglu. 2016. "A review of melatonin, its receptors and drugs." *Eurasian Journal of Medicine* 48 (2):135-141. doi: 10.5152/eurasianjmed.2015.0267.

Fallah, R., F. F. Shoroki, and F. Ferdosian. 2015. "Safety and efficacy of melatonin in pediatric migraine prophylaxis." *Current Drug Safety* 10 (2):132-135.

Force, R. W., L. Hansen, and M. Bedell. 1997. "Psychotic episode after melatonin [3]." *Annals of Pharmacotherapy* 31 (11):1408.

Fourman, L. T., and B. Robert Meyer. 2013. "Autoimmune hepatitis in association with ramelteon." *Journal of Clinical Gastroenterology* 47 (7):651-654. doi: 10.1097/MCG.0b013e31829174f0.

Gringras, P., C. Gamble, A. P. Jones, L. Wiggs, P. R. Williamson, A. Sutcliffe, P. Montgomery, W. P. Whitehouse, I. Choonara, T. Allport, A. Edmond, and R. Appleton. 2012. "Melatonin for sleep problems in children with neurodevelopmental disorders: Randomised double masked placebo controlled trial." *BMJ (Online)* 345 (7882). doi: 10.1136/bmj.e6664.

Guardiola-Lemaître, B. 1997. "Toxicology of melatonin." *Journal of Biological Rhythms* 12 (6):697-706.

Harpsøe, N. G., L. P. H. Andersen, I. Gögenur, and J. Rosenberg. 2015. "Clinical pharmacokinetics of melatonin: A systematic review." *European Journal of Clinical Pharmacology* 71 (8):901-909. doi: 10.1007/s00228-015-1873-4.

Hoebert, M., K. B. Van Der Heijden, I. M. Van Geijlswijk, and M. G. Smits. 2009. "Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia." *J Pineal Res* 47 (1):1-7. doi: 10.1111/j.1600-079X.2009.00681.x.

Hong, Y. G., and J. L. Riegler. 1997. "Is melatonin associated with the development of autoimmune hepatitis?" *Journal of Clinical Gastroenterology* 25 (1):376-378. doi: 10.1097/00004836-199707000-00020.

Illnerová, H., M. Burešová, and J. Presl. 1993. "Melatonin rhythm in human milk." *Journal of Clinical Endocrinology and Metabolism* 77 (3):838-841. doi: 10.1210/jcem.77.3.8370707.

Jain, S., and F. M. C. Besag. 2013. "Does melatonin affect epileptic seizures?" *Drug Safety* 36 (4):207-215. doi: 10.1007/s40264-013-0033-y.

Jockovich, M., D. Cosentino, L. Cosentino, R. L. Wears, and D. C. Seaberg. 2000. "Effect of exogenous melatonin on mood and sleep efficiency in emergency medicine residents working night shifts." *Academic Emergency Medicine* 7 (8):955-958.

Karasu-Minareci, E., Y. Kaya, and F. B. Yildirim. 2012. "The Achilles heel in melatonin: Asthma." *Iranian Journal of Allergy, Asthma and Immunology* 11 (3):246-251.

Kennaway, D. J. 2015. "Potential safety issues in the use of the hormone melatonin in paediatrics." *Journal of Paediatrics and Child Health* 51 (6):584-589. doi: 10.1111/jpc.12840.

Kozak, H. H., M. Boysan, A. U. Uca, A. Aydın, İ Kılınç, E. Genç, M. Altaş, D. C. Güngör, K. Turgut, and N. Özer. 2017. "Sleep quality, morningness-eveningness preference, mood profile, and levels of serum melatonin in migraine patients: a case-control study." *Acta neurologica Belgica* 117 (1):111-119. doi: 10.1007/s13760-016-0723-1.

Lardone, P. J., N. Álvarez-Sánchez, J. M. Guerrero, and A. Carrillo-Vico. 2014. "Melatonin and glucose metabolism: Clinical relevance." *Current Pharmaceutical Design* 20 (30):4841-4853. doi: 10.2174/1381612819666131119101032.

Lin, G. J., S. H. Huang, S. J. Chen, C. H. Wang, D. M. Chang, and H. K. Sytwu. 2013. "Modulation by melatonin of the pathogenesis of inflammatory autoimmune diseases." *International Journal of Molecular Sciences* 14 (6):11742-11766. doi: 10.3390/ijms140611742.

Lusardi, P., E. Piazza, and R. Fogari. 2000. "Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: A 24-hour study." *British Journal of Clinical Pharmacology* 49 (5):423-427. doi: 10.1046/j.1365-2125.2000.00195.x.

Ma, X., J. R. Idle, K. W. Krausz, and F. J. Gonzalez. 2005. "Metabolism of melatonin by human cytochromes P450." *Drug Metabolism and Disposition* 33 (4):489-494. doi: 10.1124/dmd.104.002410.

Maldonado, M. D., and J. R. Calvo. 2008. "Melatonin usage in ulcerative colitis: A case report." *J Pineal Res* 45 (3):339-340. doi: 10.1111/j.1600-079X.2008.00584.x.

Masruha, M. R., J. Lin, D. S. De Souza Vieira, T. S. C. Minett, J. Cipolla-Neto, E. Zukerman, L. C. P. Vilanova, and M. F. P. Peres. 2010. "Urinary 6-sulphatoxymelatonin levels are depressed in chronic migraine and several comorbidities." *Headache* 50 (3):413-419. doi: 10.1111/j.1526-4610.2009.01547.x.

McElhinney, D. B., S. J. Hoffman, W. A. Robinson, and J. Ferguson. 1994. "Effect of melatonin on human skin color." *Journal of Investigative Dermatology* 102 (2):258-260.

Miano, S., P. Parisi, A. Pelliccia, A. Luchetti, M. C. Paolino, and M. P. Villa. 2008. "Melatonin to prevent migraine or tension-type headache in children." *Neurological Sciences* 29 (4):285-287. doi: 10.1007/s10072-008-0983-5.

Morin, D., N. Simon, P. Depres-Brummer, F. Levi, J. P. Tillement, and S. Urien. 1997. "Melatonin high-affinity binding to alpha-1-acid glycoprotein in human serum." *Pharmacology* 54 (5):271-275. doi: 10.1159/000139495.

Nabavi, S. F., S. Habtemariam, M. Daglia, A. Sureda, E. Sobarzo-Sánchez, Z. Selamoglu, M. F. Gulhan, and S. M. Nabavi. 2017. "Melatonin and respiratory diseases: A review." *Current Topics in Medicinal Chemistry* 17 (7). doi: 10.2174/1568026616666160824120338.

Nosjean, O., M. Ferro, F. Cogé, P. Beauverger, J. M. Henlin, F. Lefoulon, J. L. Fauche, P. Delagrange, E. Canet, and J. A. Boutin. 2000. "Identification of the melatonin-binding site MT3 as the quinone reductase 2." *Journal of Biological Chemistry* 275 (40):31311-31317.

Pandi-Perumal, S. R., A. S. BaHammam, N. I. Ojike, O. A. Akinseye, T. Kendzerska, K. Buttoo, P. S. Dhandapany, G. M. Brown, and D. P. Cardinali. 2017. "Melatonin and Human Cardiovascular Disease." *Journal of Cardiovascular Pharmacology and Therapeutics* 22 (2):122-132. doi: 10.1177/1074248416660622.

Reiter, R. J., S. A. Rosales-Corral, D. X. Tan, D. Acuna-Castroviejo, L. Qin, S. F. Yang, and K. Xu. 2017. "Melatonin, a full service anti-cancer agent: Inhibition of initiation, progression and metastasis." *International Journal of Molecular Sciences* 18 (4). doi: 10.3390/ijms18040843.

Richings, C., and C. Feroz-Nainar. 2010. "Case series: Melatonin induced agitation in three patients with intellectual disability." *British Journal of Developmental Disabilities* 56 (1):77-82.

Riemersma-van der Lek, R. F., D. F. Swaab, J. Twisk, E. M. Hol, W. J. G. Hoogendijk, and E. J. W. Van Someren. 2008. "Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: A randomized controlled trial." *JAMA* -

Journal of the American Medical Association 299 (22):2642-2655. doi: 10.1001/jama.299.22.2642.

Rivara, S., D. Pala, A. Bedini, and G. Spadoni. 2015. "Therapeutic uses of melatonin and melatonin derivatives: A patent review (2012 - 2014)." *Expert Opinion on Therapeutic Patents* 25 (4):425-441. doi: 10.1517/13543776.2014.1001739.

Rubio-Sastre, P., F. A. J. L. Scheer, P. Gómez-Abellán, J. A. Madrid, and M. Garaulet. 2014. "Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening." *Sleep* 37 (10):1715-1719B. doi: 10.5665/sleep.4088.

Sagrillo-Fagundes, L., E. M. A. Salustiano, P. W. Yen, A. Soliman, and C. Vaillancourt. 2016. "Melatonin in pregnancy: Effects on brain development and CNS programming disorders." *Current Pharmaceutical Design* 22 (8):978-986.

Sajith, S. G., and D. Clarke. 2007. "Melatonin and sleep disorders associated with intellectual disability: A clinical review." *Journal of Intellectual Disability Research* 51 (1):2-13. doi: 10.1111/j.1365-2788.2006.00893.x.

Sánchez-Barceló, Emilio J., Maria D. Mediavilla, and Russel J. Reiter. 2011. "Clinical Uses of Melatonin in Pediatrics." *International Journal of Pediatrics* 2011:892624. doi: 10.1155/2011/892624.

Sandyk, R., N. Tsagas, and P. A. Anninos. 1992. "Melatonin as a proconvulsive hormone in humans." *International Journal of Neuroscience* 63 (1-2):125-135. doi: 10.3109/00207459208986662.

Seabra, Maria de Lourdes V., Magda Bignotto, Luciano R. Pinto Jr, and Sergio Tufik. 2000. "Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment." *J Pineal Res*. doi: 0.1034/j.1600-0633.2002.290401.x.

Shah, C., and A. Kablinger. 2015. "Ramelteon-induced nightmares: A case report." *Asian Journal of Psychiatry* 18:111-112. doi: 10.1016/j.ajp.2015.09.004.

Sheldon, S. H. 1998. "Pro-convulsant effects of oral melatonin in neurologically disabled children." *The Lancet* 351 (9111):1254. doi: 10.1016/S0140-6736(05)79321-1.

Singh, H. J., H. I. Saleh, S. Gupalo, and E. Omar. 2013. "Effect of melatonin supplementation on pregnancy outcome in Wistar-Kyoto and Sprague-Dawley rats." *Sheng li xue bao : [Acta physiologica Sinica]* 65 (2):149-157.

Singh, M., and H. R. Jadhav. 2014. "Melatonin: Functions and ligands." *Drug Discovery Today* 19 (9):1410-1418. doi: 10.1016/j.drudis.2014.04.014.

Smits, M. G., E. E. Nagtegaal, J. van der Heijden, A. M. L. Coenen, and G. A. Kerkhof. 2001. "Melatonin for chronic sleep onset insomnia in children: A randomized placebo-controlled trial." *Journal of Child Neurology* 16 (2):86-92.

Suhner, A., P. Schlagenhauf, R. Johnson, A. Tschopp, and R. Steffen. 1998. "Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag." *Chronobiology International* 15 (6):655-666.

Suhner, A., P. Schlagenhauf, A. Tschopp, R. Hauri-Bionda, A. Friedrich-Koch, and R. Steffen. 1998. "Impact of melatonin on driving performance." *Journal of Travel Medicine* 5 (1):7-13. doi: 10.1111/j.1708-8305.1998.tb00448.x.

Sulli, A., G. J. M. Maestroni, B. Villaggio, E. Hertens, C. Craviotto, C. Pizzorni, M. Briata, B. Seriolo, and M. Cutolo. 2002. "Melatonin serum levels in rheumatoid arthritis." *Annals of the New York Academy of Sciences* 966:276-283.

Sutherland, E. R., M. C. Ellison, M. Kraft, and R. J. Martin. 2003. "Elevated serum melatonin is associated with the nocturnal worsening of asthma." *Journal of Allergy and Clinical Immunology* 112 (3):513-517. doi: 10.1016/S0091-6749(03)01717-2.

Sutherland, E.R., R. J. Martin, M. C. Ellison, and M. Kraft. 2002. "Immunomodulatory effects of melatonin in asthma." *American Journal of Respiratory and Critical Care Medicine* 166 (8):1055-1061. doi: 10.1164/rccm.200204-356OC.

Van Geijlswijk, I. M., R. H. Mol, T. C. G. Egberts, and M. G. Smits. 2011. "Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia." *Psychopharmacology* 216 (1):111-120. doi: 10.1007/s00213-011-2202-y.

Van Geijlswijk, I. M., K. B. Van Der Heijden, A. C. G. Egberts, H. P. L. M. Korzilius, and M. G. Smits. 2010. "Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: An RCT." *Psychopharmacology* 212 (3):379-391. doi: 10.1007/s00213-010-1962-0.

Vidal. 2017. "Vidal 2017 : le dictionnaire." *92e éd*.

Wade, A. G., M. Farmer, G. Harari, N. Fund, M. Laudon, T. Nir, A. Frydman-Marom, and N. Zisapel. 2014. "Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: A 6-month, randomized, placebo-controlled, multicenter trial." *Clinical Interventions in Aging* 9:947-961. doi: 10.2147/CIA.S65625.

Wade, A. G., I. Ford, G. Crawford, A. McConnachie, T. Nir, M. Laudon, and N. Zisapel. 2010. "Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: A randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety." *BMC Medicine* 8. doi: 10.1186/1741-7015-8-51.

Welford, R. W., M. Vercauteren, A. Trebaul, C. Cattaneo, D. Eckert, M. Garzotti, P. Sieber, J. Segrestaa, R. Studer, P. M. Groenen, and O. Nayler. 2016. "Serotonin biosynthesis as a predictive marker of serotonin pharmacodynamics and disease-induced dysregulation." *Sci Rep* 6:30059. doi: 10.1038/srep30059.

Whittom, S., M. Dumont, D. Petit, A. Desautels, B. Adam, G. Lavigne, and J. Montplaisir. 2010. "Effects of melatonin and bright light administration on motor and sensory symptoms of RLS." *Sleep Medicine* 11 (4):351-355. doi: 10.1016/j.sleep.2009.12.008.

Xu, J., L. L. Wang, E. B. Dammer, C. B. Li, G. Xu, S. D. Chen, and G. Wang. 2015. "Melatonin for Sleep Disorders and Cognition in Dementia: A Meta-Analysis of Randomized Controlled Trials." *American Journal of Alzheimer's Disease and other Dementias* 30 (5):439-447. doi: 10.1177/1533317514568005.

ANNEX 1

Presentation of participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP

Chair

Mr Alexandre MACIUK – University Lecturer (Paris-Sud University) – Speciality: pharmacognosy

Members

Ms Catherine ATLAN – University Lecturer – Hospital Practitioner (Luxembourg Hospital Centre) – Specialities: metabolic diseases, nutrition and endocrinology

Mr Alain BOISSONNAS – Retired, University Professor – Hospital Practitioner (University Hospital Paris-Sud) – Speciality: general medicine

Ms Sabrina BOUTEFNOUCHET – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Mr Pierre CHAMPY – University Professor (Paris-Sud University) – Speciality: pharmacognosy

Mr Pascal CRENN – University Professor – Hospital Practitioner (Raymond Poincaré Hospital) – Speciality: hepato-gastroenterology

Mr Thierry HENNEBELLE – University Professor (Lille II University) – Speciality: pharmacognosy

Ms Raphaële LE GARREC – University Lecturer (University of Western Brittany) – Speciality: toxicology

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Speciality: allergology

Ms Dominique Angèle VUITTON – Retired, University Professor – Hospital Practitioner (University of Franche Comté) – Specialities: allergology, hepato-gastroenterology

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

Mr Jean-Fabien ZAZZO – Retired, Hospital Practitioner (Antoine Béclère Hospital) – Specialities: general medicine, nutrition

RAPPORTEURS

Mr Thierry HENNEBELLE – University Lecturer (Lille II University) – Speciality: pharmacognosy

Ms Raphaële LE GARREC – University Lecturer (University of Western Brittany) – Speciality: toxicology

EXPERT COMMITTEE

The work that is the subject of this report was monitored and adopted by the following Expert Committee:

- CES on "Human Nutrition" – 2015-2018

Chair

Mr François MARIOTTI – Professor (AgroParisTech) – Specialities: metabolism of proteins, amino acids, nutritional requirements and recommendations, postprandial metabolism, cardiometabolic risk

Members

Ms Catherine ATLAN – Doctor (Luxembourg Hospital Centre) – Specialities: endocrinology, metabolic diseases

Ms Catherine BENNETAU-PELISSERO – Professor (Bordeaux Sciences Agro) – Specialities: phyto-oestrogens, isoflavones, endocrine disruptors, bone health

Ms Marie-Christine BOUTRON-RUAULT – Research Director (CESP Inserm) – Specialities: nutritional epidemiology and cancer, digestive system

Mr Jean-Louis BRESSON – University Professor – Hospital Practitioner (AP-HP Necker Hospital – Sick Children, Centre for Clinical Investigation 0901) – Specialities: epidemiology, immunology, infant nutrition, pregnant women and proteins

Mr Olivier BRUYERE – University Professor (University of Liège) – Specialities: epidemiology, public health, osteoporosis

Ms Blandine DE LAUZON-GUILLAIN – Research Manager (Inserm, CRESS, Villejuif) – Specialities: epidemiology, infant nutrition, nutrition of pregnant and breastfeeding women, public health

Ms Anne GALINIER – University Lecturer – Hospital Practitioner (Paul Sabatier University – Toulouse University Hospital) – Specialities: metabolism of adipose tissue/obesity, pathophysiology

Mr Jean-François HUNEAU – Professor (AgroParisTech) – Speciality: human nutrition

Ms Emmanuelle KESSE-GUYOT – Research Director (INRA, UMR Inserm U1153/INRA U1125/CNAM/University of Paris 13) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health

Ms Corinne MALPUECH-BRUGERE – University Lecturer (University of Auvergne) – Speciality: disease nutrition, metabolism of macro- and micronutrients

Ms Catherine MICHEL – Research Manager (INRA, UMR INRA/University, Nantes) – Specialities: infant nutrition, intestinal microbiota, colic fermentation, prebiotics

Ms Beatrice MORIO-LIONDORE – Research Director (INRA Lyon) – Specialities: human nutrition, energy metabolism

Ms Jara PEREZ-JIMENEZ – Contract Researcher (ICTAN – CSIC, Madrid) – Specialities: micro-constituents, nutrition and pathologies, bioavailability

Mr Sergio POLAKOFF – Research Manager (INRA Clermont-Ferrand/Theix) – Specialities: nutrition and pathologies, nutrition and public health, energy metabolism

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Specialities: allergology

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Nice Sophia Antipolis) – Specialities: nutrition and physical activity, bioavailability, oxidative stress

Mr Luc TAPPY – University Professor – Hospital Practitioner (University of Lausanne) – Specialities: endocrinology, metabolism of carbohydrates

Mr Stéphane WALRAND – Research Director (INRA Clermont-Ferrand/Theix) – Specialities: pathophysiology, protein metabolism and amino acids

ANSES PARTICIPATION

Scientific coordination

Ms Fanny HURET – Scientific Project Leader for Nutrivigilance – Risk Assessment Department

Scientific contribution

Ms Charlotte LEGER – Scientific Project Leader for Nutrivigilance – Risk Assessment Department

Ms Gwenn VO VAN-REGNAULT – Nutrivigilance Project Officer – Risk Assessment Department

Ms Irène MARGARITIS – Head of the Nutritional Risk Assessment Unit – Seconded University Professor (University of Nice Sophia Antipolis) – Risk Assessment Department

Administrative assistance

Ms Virginie SADE – Risk Assessment Department