CIVIL AVIATION AUTHORITY

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MELATONIN: RECOMMENDATIONS CONCERNING ITS USE BY AIRCREW

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Executive summary

Introduction

This review was carried out for the Safety Regulation Group of the CAA under contract number 7D/S/952/1, as part of a programme of research into the sleep and wakefulness of the airline pilot.

It has emerged that some aircrew are using melatonin to aid adaptation to time-zone changes and to assist sleep in on-board rest facilities. The extent of this use is unknown. The use of a compound which has not undergone detailed pre-clinical development is of particular concern.

Efficacy of melatonin in jet lag

Studies reporting beneficial effects of melatonin in the treatment of jet lag have been based largely upon improvements in subjective assessments, with only two studies monitoring physiological rhythms. There is a general consensus from laboratory investigations that melatonin does have circadian phase shifting properties. Little or no information is available on the effect of melatonin upon objective measures of performance and sleep in the field. In the laboratory, the observed effects of melatonin on sleep have been inconsistent.

Widely differing doses have been evaluated and the minimum effective dose and preparation (immediate or sustained release) of melatonin has not been established. Recommendations available to the general public concerning the timing and length of treatment are not based on systematic studies.

Adverse effects of melatonin

Melatonin causes sleepiness and impaired performance immediately after ingestion and in some doses it may be associated with residual sequelae. Inappropriate timing of melatonin administration leads to disturbance of sleep and undesirable shifts in circadian rhythms.

Toxicological data for melatonin are incomplete. Its inhibitory effects on the reproductive system indicate potential adverse effects upon fertility.

Recommendations

Melatonin is not recommended for use by aircrew. Aircrew should be warned formally about its adverse effects. Its use 12h before a duty period and on-board the aircraft should be forbidden.

If and when synthetic melatonin analogues, which have undergone toxicological testing and phase III clinical trials, receive a product licence, the available information relating to their efficacy in the treatment of jet lag should be reviewed.

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1 INTRODUCTION

1.1 Terms of reference

This review was carried out for the Safety Regulation Group of the CAA under contract number 7D/S/952/1, as part of a programme of research into the sleep and wakefulness of the airline pilot.

1.2 Background

1.2.1 It has emerged that some aircrew are using melatonin to aid adaptation to time-zone changes and to assist sleep in on-board rest facilities. The extent of this use is unknown. It has occurred at a time when unsubstantiated claims in the media for the anti-ageing properties of melatonin have led to an explosion of its use by the general public, with estimates as high as 20 million users world-wide. Melatonin has also been used to alleviate insomnia and problems associated with the desynchronisation of the day-night cycle which occur during shift work and following transmeridian travel and also in the blind.

1.2.2 In the UK, melatonin is available only under strict medical supervision on a named-patient basis. However, in the USA and some other countries it is classed as a foodstuff/dietary supplement and it is readily available in health food stores and at airports. Some of the preparations available will be described in this report. This classification has avoided the need for the toxicological evidence required before a medicinal product is cleared by the regulatory authorities and given a product licence. This information is unlikely to become available because the costs of gathering such data would normally fall to the pharmaceutical company owning the patent for a drug. The repetitive use of a compound which has not been fully investigated is of particular concern and this report will summarise any possible harmful effects.

1.3 Melatonin physiology

1.3.1 Melatonin is the principal hormone of the pineal gland and its synthesis from tryptophan via serotonin is under adrenergic control[1]. Its secretion is controlled by the suprachiasmatic nuclei of the hypothalamus which receive information detected by the retina about the dark-light cycle. Melatonin may also regulate its own secretion which normally begins in the late evening, before the nocturnal increase in sleepiness[2]. It then peaks after midnight at mean plasma levels of around 80 pg/ml (range 0-200 pg/ml) and decreases towards the end of the sleep period[3,4]. The circadian rhythm of melatonin is highly reproducible for a particular individual, though there is considerable variation in melatonin levels between different individuals and ageing is associated with reduced melatonin secretion[1].

1.3.2 The nocturnal secretion of melatonin lowers body temperature, as does the administration of exogenous melatonin, though the mechanism by which this occurs is not yet clear[5]. Core temperature is known to be relevant to sleep induction and it has been suggested that melatonin exerts a hypnotic effect through thermoregulatory mechanisms[6]. However, the episodic secretion of melatonin is not related to a particular stage of sleep[7].

1.3.3 Light of suitable intensity and spectral composition is able to suppress melatonin production[8] and to reset the human circadian clock by an amount dependent upon the time of administration[9,10]. For example, light exposure prior to the body temperature minimum

will phase delay circadian rhythms, whereas light after the temperature minimum will induce a phase advance. Light in the afternoon has little or no effect on circadian phase. Exogenous melatonin is reported to counter the ability of bright light to increase temperature[11] and induce phase shifts[5]. Indeed, the effect of melatonin administration upon circadian rhythms is the opposite of the effect of bright light[12,13]. Melatonin delays the phase of circadian rhythms when given in the morning and advances the phase of circadian rhythms when administered in the afternoon or early evening.

2 EFFICACY OF MELATONIN IN JET LAG

2.1 Sleep

2.1.1 *Sleep disturbance after transmeridian travel:* The severity of sleep disturbance following a time zone change is dependent upon the direction of travel, the number of time zones crossed and the timing of the flight itself[14].

2.1.2 *Eastward:* After an eastward journey, when sleep is scheduled in advance of the 'home' bedtime, difficulty in falling asleep may be accompanied by increased wakefulness in the early part of the night. However, these changes may not be apparent on the first night in the new time zone if the flight involves overnight travel without sleep. Problems with sleep may continue for several days after the flight, with reductions in rapid eye movement (REM) sleep and possibly slow-wave sleep, and this may be followed by a compensatory increase in REM sleep several nights later.

2.1.3 *Westward*: Sleep disturbance after a westward flight is usually less persistent, lasting perhaps two or three days. Sleep is likely to be of good quality in the early part of the night, with increased slow-wave activity on the first night due to the delay to the first rest period. On subsequent nights, when the pressure for slow-wave sleep is less, there may be an increase in REM sleep as bedtime corresponds with early morning in the 'home' time zone, when REM sleep predominates. Awakenings may occur towards the end of the night, at a time corresponding to daytime in the 'home' time zone.

2.1.4 *Sleep promotion:* Given the adverse effects of sleep loss on alertness and performance, substances which have sleep promoting properties may be useful in the management of jet lag, provided they are without residual sequelae.

2.1.5 *Hypnotic activity of melatonin in the home time zone:* Laboratory studies investigating the hypnotic activity of melatonin in healthy man have yielded inconsistent results with respect to dose. This is most likely related to variations in methodology, in particular, to the time of melatonin administration and the age of the subjects.

2.1.6 In electroencephalographic (EEG) studies of nocturnal sleep in the home time zone, an improvement in sleep efficiency was reported with 80 mg melatonin given 1.5h before bedtime to young subjects with situational insomnia induced by traffic noise[15]. Sleep efficiency also increased with 1 and 0.3 mg melatonin administered to young subjects 1h prior to bedtime[16] and with 1 mg given to middle aged subjects 2h prior to bedtime[17]. Changes in REM sleep were observed with 5 mg melatonin given 15 min before bedtime to individuals ranging in age from 21 to 40 years[18]. Two of these studies found no effects of the lower doses tested (0.3 mg[17] and 1 mg[18]). However, there were no changes in subjectively assessed sleep after melatonin treatment in the three studies where this was recorded[15,17,18].

2.1.7 Another investigation reported improved subjective sleep quality and a change in sleep microstructure (the cyclic alternating pattern of arousal), when melatonin was given to young subjects 0.5h prior to bed[19]. However, no changes in classical EEG measures were observed. Preliminary results from a recent study also found no effect of melatonin (0.1 to 10 mg) upon sleep architecture when given at bedtime (2330h) to young subjects (Nicholson, Stone and Turner, unpublished data). Subjective sleep measures were also unchanged by melatonin.

2.1.8 It would appear that changes in nocturnal sleep are more likely to be observed when melatonin is given prior to the time of endogenous secretion. Deacon and Arendt[20] reported that melatonin given in the early evening (7h before bedtime) to young subjects resulted in a dose related (0.05 to 5 mg) improvement in subjective sleep quality. The subjects avoided exposure to bright light for two days preceding melatonin administration and this may have contributed to the more marked effects of the drug reported in this study.

2.1.9 Daytime sleep, which is less restful than nocturnal sleep, would appear to be improved by melatonin, with reductions in sleep latency and an increase in sleep efficiency[21,22]. It has been suggested that these hypnotic effects of melatonin during the day may be associated with its hypothermic properties[5].

2.1.10 In summary, melatonin, unlike the benzodiazepines, does not have consistent, dose-related effects on sleep.

2.1.11 *Hypnotic activity of melatonin in the field:* Several placebo controlled investigations which report beneficial effects of melatonin upon subjective jet lag have also monitored sleep subjectively[23-27]. Of those studies using subjects adapted to local time before travel [23-25], two investigated an eastward time zone change only. Melatonin (5 mg), given in the evening for 3 days prior to, and for 4 days at bedtime following, an 8h eastward transition, improved subjective sleep quality of individuals aged from 29 to 68 years (mean age 48.5 ±2.2 SEM)[23]. However, an 8 mg dose administered to younger subjects (mean age 36 ±7.7 SD) on the day preceding, and for 3 days at bedtime following, an overnight eastward flight across 6 to 11 time zones, had no effect on sleep[25].

2.1.12 In an investigation of 12h time zone transitions, both eastward and westward, using volunteers aged 28 to 68 years, 5 mg melatonin given for 3 days preceding, during, and for 3 days after the flight reduced the time taken to re-establish a normal sleep pattern, though it had no effect on sleep duration[24]. Jet lag ratings were worse after the westward journey for all subjects, irrespective of treatment. However, it is not clear whether statistical analysis of the data included comparison of melatonin and placebo treatment with respect to the direction of travel. Beneficial effects of melatonin on sleep patterns and jet lag were reported only for the trip as a whole.

2.1.13 In a study using military personnel aged 24 to 41 years, subjects took 10 mg melatonin to phase advance sleep prior to travel and to assist adaptation to night operations in the destination time zone which was 8h in advance of home time[27]. In addition to advancing the timing of sleep, melatonin increased sleep duration, as measured using actigraphy.

2.1.14 A reduction in subjective sleep disturbance was reported by cabin crew (age range 25-52, mean 34.9 ±7.7SD) who took 5 mg melatonin for 5 days after returning from a 9 day trip (Auckland – Los Angeles – London – Los Angeles – Auckland)[26]. However, in the same study another group who took melatonin during the layover in Los Angeles, on the final flight and upon arrival home reported sleeping difficulties (Section 4.3).

2.1.15 There have been two field studies investigating the use of melatonin to assist adaptation to shiftwork[28,29], though only one of these monitored sleep. A 5 mg dose prior to daytime sleep during a period of seven consecutive night shifts was reported to improve sleep quality and quantity assessed subjectively[28].

2.1.16 In summary, there is a lack of information on the effect of melatonin in the field upon objective measures of sleep. Field trials completed to date have generally reported that melatonin improves subjective sleep. However, for reasons of cost, few studies have addressed differences in the direction of travel and none has used subjects as their own control in a repeated cross-over design. Various time zones have been investigated, sometimes within the same study without differentiating between the magnitude of the transition. Some trials have used a wide age range of subjects whose sleep may have differed considerably, since increasing age is known to be associated with a deterioration in sleep quality and quantity. Compliance with investigators' instructions may have been poorer in subjects travelling to attend meetings and conferences than in those recruited solely for the purposes of a jet lag study.

2.1.17 *Hypnotic activity of melatonin after a simulated phase change:* In the only EEG study investigating the efficacy of melatonin in assisting adaptation to a phase shift, a 5 mg dose increased sleep duration, efficiency and stage 2 sleep on the first of three nights of administration to young subjects (21-29 years) after a 9h phase advance[30]. However, in spite of the greater time spent asleep, the duration of slow wave sleep was not only less than baseline but also less than placebo. Interestingly, no subjective changes in sleep were found in this study or in an earlier laboratory simulation of a 9h phase advance which also used young subjects (20-32 years) and a 5 mg dose[31]. However, a previous study using the identical protocol to Stone *et al*[30] reported beneficial effects of melatonin on the subjective sleep of young subjects (22-26 years)[32].

2.1.18 In a study simulating night shiftwork, melatonin was reported to improve daytime sleep quality, assessed using actigraphy, in young subjects (18-30 years)[33]. However, in an attempt to maintain plasma melatonin levels, the drug was given in a divided dose (2 mg before bedtime, 1 mg at 2 and 5h after bedtime) which would have disrupted sleep.

2.2 Circadian rhythms

2.2.1 A number of studies suggest that melatonin has phase shifting properties in man. Two field studies have reported that 5 mg melatonin accelerated adaptation of the circadian rhythm of some physiological variables following an eastward flight[23,34]. Melatonin hastened adaptation of the cortisol rhythm following an 8-9h and a 10-11h, but not a 6-7h, eastward time zone change in young subjects (22-37 years, mean 26±3SD)[34]. However, melatonin administration did not change either the endogenous melatonin rhythm or subjectively rated jet lag. Arendt *et al*[23] studied subjects from a wider age range and administered melatonin before, as well as following, an 8h eastward time zone transition. This study found faster adaptation of both melatonin and cortisol rhythms and reduced subjective jet lag. Similarly, in a study of night shift workers, 0.5 mg melatonin prior to daytime sleep resulted in phase-shifting of the endogenous melatonin rhythm[29].

2.2.2 A laboratory simulation of a 9h eastward time zone transition, which used more frequent sampling rates to achieve a more accurate estimate of circadian parameters, found that 5 mg melatonin enhanced the resynchronisation speed of temperature, melatonin, cortisol, potassium and sodium but not calcium rhythms in young subjects (20-32 years)[31]. Subsequently, two laboratory studies have shown that melatonin given at different times of the day influences the timing of endogenous melatonin production[12,13]. These studies

describe a phase-response curve for melatonin whereby administration of melatonin in the morning delays circadian rhythms while melatonin given in the afternoon or early evening advances rhythms.

2.2.3 Evening administration of melatonin has been reported to change the onset of melatonin secretion and the timing of sleep onset in a dose related manner[20]. In another study, melatonin (5 mg given in the evening) was shown to synchronise, over a period of several days, the sleep-wake pattern and temperature rhythm in most subjects who had 'free running' circadian rhythms as a result of living in constant dim light[35].

2.2.4 It has been suggested that the effects of melatonin are likely to be more marked in the laboratory than in the field where bright light and other time cues may counter its influence[31]. Deacon and Arendt[32] addressed this issue and found that, in a simulated 9h phase advance, bright light did not affect the phase-shifting properties of melatonin. However, as the authors note, melatonin was given before exposure to bright light and it remains to be tested whether light preceding melatonin treatment does counter the effects of melatonin.

2.2.5 In summary, there is a general consensus in the literature that melatonin does have phase shifting properties, though effects on sleep have been inconsistent. However, all laboratory and field studies bar one have used subjects who, unlike aircrew, were adapted to the sleep-wake cycle in the laboratory or to local time before undergoing a phase shift. The effects of melatonin upon the sleep and circadian rhythms of those who frequently undergo rapid time zone transitions may be quite different and this is discussed further in Section 4.3.

3 ADVERSE EFFECTS OF MELATONIN

3.1 Side effects

3.1.1 No clinical trials have been carried out upon melatonin and the true incidence of adverse effects among the many users in the USA is unknown, as there is no requirement for formal reporting and monitoring procedures for substances classified as a dietary supplement. An informal survey on the world-wide web found that although 10% of melatonin users reported no beneficial effects of the substance, a further 10% complained of nightmares, headaches, morning grogginess, mild depression and low sex drive[36]. The same article reports four unsubstantiated complaints to the FDA concerning disrupted sleep patterns, nausea and genital pain with melatonin administration.

3.1.2 In a series of placebo controlled field studies assessing the efficacy of melatonin in jet lag in 586 healthy volunteers, (474 taking 5mg melatonin, 112 taking placebo), the following side effects were reported: sleepiness (melatonin 8.3%; placebo 1.8%), headache (melatonin 1.7%; placebo 2.7%), nausea (melatonin 0.8%; placebo 0.9%), 'fuzziness/giddiness' (melatonin 0.6%; placebo 0%) and light headedness (melatonin 0.8%; placebo 0%)[37]. The only significant side effect was sleepiness.

3.1.3 Melatonin is promoted by some manufacturers or suppliers as a naturally occurring substance which is safer than prescription drugs such as the benzodiazepines. This argument may be particularly attractive to aircrew but they should be made aware that naturally occurring substances are not necessarily safe e.g. androgens. Furthermore, whilst prescription drugs such as temazepam or zolpidem should be used with caution and

under strict medical supervision in the treatment of jet lag, they have, unlike melatonin, undergone pre-clinical development.

3.2 Alertness and performance

3.2.1 There is general agreement in the literature that immediate effects of melatonin include reduced levels of alertness and performance impairment. A 1.7 mg dose given intranasally in the morning (0900-1000h) led to sleep in 70% of young subjects[38]. In a group of subjects from a wider age range (18-45 years), 240 mg melatonin (given in a divided dose between 1200-1400h) increased subjective sleepiness and impaired performance up to 2h post ingestion[39]. Administration of melatonin (10 to 80 mg) close to midday reduced vigilance 2.25h after ingestion[40]. Lower doses (0.1 to 10 mg), also given around midday, reduced sleep latency, measured using a pressure switch, 1.75h post-ingestion[41]. In the same study, 1 and 10 mg doses also impaired performance on a vigilance task 2.25h after administration.

3.2.2 EEG studies have shown increased spectral power in the frequency bands associated with sleep following administration of 5 mg melatonin, on separate occasions, at 1200, 1700, 1900 and 2100h. Peak effects were observed more rapidly the later the time of melatonin administration[42].

3.2.3 While some studies have found no residual effects of up to 10 mg melatonin on performance (Nicholson, Stone and Turner, unpublished data), others have reported adverse effects on memory (5 mg dose[28] 1 to 40 mg doses[43]) and vigilance (10 mg dose[44]). Sustained release preparations have not been widely evaluated in the laboratory and may be more likely to lead to residual effects[22].

3.3 Sleep and circadian rhythms

3.3.1 In a study designed to investigate the effectiveness of melatonin in synchronising free-running circadian rhythms, a daily dose (5mg) given at 2000h to 16 healthy young men living in constant dim light for 11 to 16 days led to a highly irregular sleep pattern in four subjects whose core body temperature maximum was close to the time of drug ingestion[45]. The authors suggest that in the absence of strong time cues, melatonin may have disrupted and uncoupled the timing mechanisms for sleep onset and offset by acting as a signal for sleep onset.

3.3.2 In a laboratory simulation of a 9h eastward time zone change, although melatonin (5 mg) changed the direction of adaptation from a delay to an advance shift in two out of eight subjects, it resulted in a slower resynchronisation of the endogenous melatonin rhythm in one individual[31]. Similarly, cabin crew given 5 mg melatonin prior to and during the final flight of a 9 day trip (see section 3.1.14), and for five nights after returning home, reported more severe jet lag than those crew given melatonin only upon arrival home[26]. Arendt *et al*[46] also reported that, in a field trial, four out of 52 subjects crossing eight time zones felt worse after melatonin than placebo.

3.3.3 These adverse effects are most likely due to administration of melatonin at an inappropriate time in the subjects' endogenous melatonin circadian cycle[31]. As Lewy *et al*[12] note, there is a cross-over region of the melatonin phase-response curve, corresponding to a clock time of around midday, where melatonin administration prior to this time will result in a phase delay while ingestion after this time will elicit a phase advance. Thus, instructions to treat jet lag with ingestion of melatonin at a particular

clock time may not correspond with the appropriate circadian time, particularly in aircrew who may not even be adapted to the home time zone before a trip.

3.3.4 Two studies suggest that melatonin may affect circadian rhythms following cessation of treatment. A preliminary report in psychiatric patients indicates that withdrawal of melatonin can lead to 'free run' of circadian rhythms[47]. Six out of nine healthy volunteers living in constant dim light who were given 5mg melatonin daily for two weeks shortened the period of their circadian rhythm after replacement of melatonin with placebo[35].

3.4 Reproductive function

3.4.1 The reproductive effects of melatonin in man have been reviewed by Arendt[47]. Low doses (2 mg) of melatonin administered to healthy subjects in the early evening for one month altered the timing of prolactin secretion. Higher doses (80 to 100 mg) substantially increased prolactin secretion. In another study melatonin potentiated testosterone suppression of luteinizing hormone in men. There are also reports that high doses lower sperm motility in rodents. However, studies in man using lower doses show no such evidence. Preliminary findings from a recent study indicated that melatonin (10 mg) administered at 1300h for seven days during the late follicular and early luteal phase of the menstrual cycle reduced cycle length, though no such change occurred when the substance was given at 2300h[48].

3.4.2 Melatonin is therefore inhibitory to some aspects of human reproductive function. Indeed, clinical trials have investigated the use of melatonin (75mg) combined with norethindrone (0.5mg) as a contraceptive pill. Furthermore, melatonin crosses the placenta and, though there is no evidence at the present time, it may have effects on the foetus or on subsequent development, particularly the onset of puberty.

3.5 The eye

Melatonin in large doses has been found to potentiate retinal damage induced by bright light in rats[49], though there was no evidence of retinal toxicity when 1g per day was given for one month to patients with hyperpigmentation [50].

3.6 The cardiovascular system

Melatonin administration in animals can lead to transient hypotension[51]. There is little information available on the cardiovascular effects of melatonin ingestion in man, though endogenous melatonin has been reported to be lower in patients with cardiovascular disease[52].

3.7 Tumours

Melatonin has been reported in some studies to induce tumours and in others to have an inhibitory effect on tumours in animals[47]. Further research in this area is required.

3.8 Drug interactions

The onset and the levels of endogenous melatonin secretion are influenced by drugs acting via noradrenergic and serotonergic systems[47]. For example, β-adrenoceptor antagonists are known to inhibit melatonin production and blunt the nocturnal decline in body temperature, an effect which can be antagonised by co-administration of melatonin[5].

However, there is no published information on side effects arising from the combined use of melatonin with this or any other class of medication.

4 MELATONIN PREPARATIONS AVAILABLE

4.1 In the UK the Committee for Safety of Medicines has banned over-the-counter sales of melatonin as it is a medicinal product and requires a product licence. However, the compound is available via the world-wide web (Appendix) and in the USA from health food shops, pharmacies, supermarkets and mail order catalogues. Many unsubstantiated claims are made by suppliers about beneficial effects of melatonin or its lack of harmful effects.

4.2 The facilities and production methods of laboratories manufacturing melatonin are not subject to regulation by the Food and Drugs Administration in the USA. There is no guarantee of the purity, quality or contents of a preparation, indeed, tests found some preparations contained no melatonin[53]. Preparations derived from animal pineal glands are associated with a risk of transmission of animal viruses. The pharmacological activity of preparations containing other additives is unknown and these substances may have adverse effects and residual sequelae.

5 CONCLUSIONS

5.1 Studies reporting beneficial effects of melatonin in the treatment of jet lag have largely been based upon subjective assessments, with only two studies monitoring physiological rhythms. There is a general consensus from laboratory investigations that melatonin does have circadian phase shifting properties. Little or no information is available on the effect of melatonin upon objective measures of performance and sleep in the field. In the laboratory, the observed effects of melatonin on sleep have been inconsistent.

5.2 Widely differing doses have been evaluated and the minimum effective dose and preparation (immediate or sustained release) of melatonin have not been established. Recommendations available to the general public concerning the timing and length of treatment are not based on systematic studies.

5.3 Inappropriate timing of melatonin administration leads to disturbance of sleep and undesirable shifts in circadian rhythms. Melatonin causes sleepiness and impaired performance immediately after ingestion and it may also have residual sequelae. The activity of melatonin preparations containing other additives is unknown.

5.4 Toxicological data for melatonin is incomplete and information on possible drug interactions is lacking. Its inhibitory effects on the reproductive system indicate potential adverse effects upon fertility.

6 RECOMMENDATIONS

6.1 Melatonin is not recommended for use by aircrew. Aircrew should be formally warned about its adverse effects, in particular its potential to increase the severity of jet lag, its effects on performance and its effects on reproductive function and fertility. The use of melatonin 12h before a duty period and on-board the aircraft should be forbidden.

6.2 If and when synthetic melatonin analogues, which have undergone toxicological testing and phase III clinical trials, receive a product licence, the available information relating to their efficacy in the treatment of jet lag should be reviewed. However, without an accurate estimate of an individual's internal circadian phase, such analogues may still be unsuitable for routine use by aircrew.

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Appendix A Melatonin preparations available

Table A-1; Availability of melatonin via the world wide web

Product name and supplier	*Melatonin dose and source*	*Other constituents*	*Directions /precautions/ contraindications (C/I) provided by supplier*	*Information provided by supplier*
Natural sleep supplied by Life Extension International.	5 mg sustained release synthetic melatonin.			Melatonin has been shown by medical studies to ease insomnia, combat jet lag and boost the immune system. Ongoing studies suggest that supplementing this hormone may even extend life expectancies while staving off the ravages of ageing.
Somniset supplied by Life Plus.	1.5 mg melatonin. Source not stated but most likely derived from animal pineal glands (see other constituents).	Minerals, herbs, amino acids, calcium lactate, valerian root, L-Glutamate, Mg glutamate, hops, L-glutamic acid, zinc gluconate, passion flower, L-tyrosine, concentrated tissue nutrients: pineal, brain, hypothalamus, pituitary.	1 to 5 tablets 0.5h before bedtime. Start with one or two tablets and increase as needed after 3 nights. More is not necessarily better.	Several days supplementation may be needed to begin seeing results. It is not a drug and the common sleeping pill morning hangover does not occur. Insomnia exists when melatonin levels are low or when it is produced at the wrong time. Supplementing can help re-establish balance and help you to set your biological clock.

Table A-1; Availability of melatonin via the world wide web (continued)

Product name and supplier	*Melatonin dose and source*	*Other constituents*	*Directions /precautions /contraindications (C/I) provided by supplier*	*Information provided by supplier*
Melatonin supplied by New Way International Inc.	0.3 mg and 1 mg synthetic melatonin.		1 to 2 tablets at bedtime. C/I: pregnancy, lactation, autoimmune conditions, depression; children under 16. Drug interactions: steriods; Adverse drug reactions: drowsiness. Do not take this product when driving or operating machinery.	FDA registered manufacturing facilities.
Natrol supplied by Natural Life Nutrition.	3 mg and 3 mg sustained release melatonin. Source not stated.	None stated.		
Melatonin supplied by Pure International.	3 mg 'pure' melatonin.	Vitamin B6.	One half to one tablet daily, preferably 0.5h before bedtime.	Scientists in labs all over the world are also investigating the role of melatonin in treating specific ailments. For example: jet lag, insomnia, psychological, anti-ageing, enhancing immune system and more.
Pathway supplied by melatonin Pathway.	3 mg synthetic melatonin.		1 to 2 capsules before bedtime/ as directed by physician. Many people have reported vivid dreams while taking melatonin. Some people get groggy when they have taken supplemental melatonin – indicating that finding the correct dosage is important.	Melatonin is very non-toxic even in large doses (>7500mg).
Product name and supplier	Melatonin dose and source	Other constituents	Directions /precautions /contraindications (C/I) provided by supplier	Information provided by supplier

Table A-1; Availability of melatonin via the world wide web (continued)

Product name and supplier	*Melatonin dose and source*	*Other constituents*	*Directions /precautions /contraindications (C/I) provided by supplier*	*Information provided by supplier*
Melapure supplied by Genzyme Pharmaceuticals.	3 mg and 3 mg sustained release synthetic melatonin.	Available with and without vitamin B-6.		[The] connection between melatonin levels and the quality of sleep has contributed to interest in melatonin as a natural sleeping aid. Melatonin may also benefit travellers crossing time zones and shift workers experiencing disrupted sleep patterns. Melatonin is produced in Genzyme's pharmaceutical facilities.
Melatonin Ultra supplied by Free Life Products.	1 mg synthetic melatonin sub-lingual tablet.	Kava root, chamomile flower, hops fruit, peppermint leaf, lemon balm leaf, valerian root, skullcap herb.	1 to 5 tablets 0.5h before bedtime.	
E-Z Sleep supplied by Body Systems Technology Inc.	3 mg melatonin. Source not stated.		1 to 2 capsules 1h before bed. Effectiveness of doses may vary. Vivid dreams could be common.	Helps these conditions: difficulty sleeping, chronic insomnia that requires a drug, anxiety disorder requiring anti-anxiety drug, jet lag, regular shift changes at work.

Table A-1; Availability of melatonin via the world wide web (continued)

Product name and supplier	*Melatonin dose and source*	*Other constituents*	*Directions /precautions /contraindications (C/I) provided by supplier*	*Information provided by supplier*
Melatonin supplied by PUR-US / TRM Inc.	3 mg synthetic melatonin.	Vitamin B6.	As a dietary supplement 1 tablet 20min before bedtime. Warning: persons with a medical condition or taking monoamine oxidase inhibitors, pregnant or lactating women should consult physician before use.	Nature's answer to deeper, healthier, rejuvenating sleep. Proven to eliminate jet lag.
Melatonin supplied by World Wide Labs.	0.3 mg and 1.5 mg tablet, 1.5 mg and 3 mg sustained release tablet, 1 mg liquid.		Melatonin to be taken prior to a flight and 0.5h before bedtime. Melatonin taken before travel can actually worsen symptoms. A 0.3 mg dose for beginners & those in need of getting to sleep and for jet lag. Melatonin 1.5 mg for normal insomnia. A 3 mg dose for tougher sleeping problems. Liquid form is easy to swallow & handy for experimenting with varied dosages. The appropriate dose can vary and successful results have been achieved with doses ranging from 0.1mg to 200 mg. Start off small (less than 0.5 mg) each night before bedtime, and work your way to larger doses if needed. If you wake up feeling a little tired you should reduce your dosage. 10% of users reported nightmares, headaches, morning grogginess, mild depression & low sex drive. C/I: fluoxetine.	Studies suggest that low dose supplements can hasten sleep and ease jet lag, without the hazards or side effects of prescription sleeping pills. Researchers have given people up to 600 to 3000 times the usual doses – without causing any toxicity. High doses, while causing no immediate harm, could have unknown long-term effects.
Sweet Dreams supplied by For*mor International.	Not stated.	Valerian root, passion flower,skullcap, wood betony, hops, chamomile flower.	One capsule before bed or as recommended. C/I pregnancy, lactation, autoimmune conditions, depression, children under 16 years unless recommended by your health care professional.	Potential benefit to induce sleep; helps with symptoms of jet lag; may fight depression in the elderly; regular doses after age 60 may enhance life span by as much as 20 years.

Table A-1; Availability of melatonin via the world wide web (continued)

Product name and supplier	*Melatonin dose and source*	*Other constituents*	*Directions /precautions /contraindications (C/I) provided by supplier*	*Information provided by supplier*
Source Natural Brand supplied by Tenzing Momo Inc.	1 and 5 mg; 2 mg sustained release melatonin. Source not stated.		C/I: severe allergies, autoimmune diseases or immune system cancers, lactation, pregnancy, women trying to conceive.	
Melatonin supplied by Vitamin Research Products Inc.	0.75, 3 and 10mg synthetic melatonin.		C/I: children, adolescents, pregnancy, lactation. Dosage varies according to an individual's sensitivity and age.	Melatonin is most widely used for relieving sleep disorders, insomnia and jet lag. It is also used because of its ability to enhance the immune system.