DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Scientific Memorandum

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To: the file, [redacted]

Subject: Update on the review of the safety of melatonin use as an ingredient in conventional foods

The purpose of this memorandum is to provide an update on the previous review of the safety of melatonin use as an ingredient in conventional foods (dated July 25, 2011).

For this purpose, I have searched PubMed, Science Direct, and Quertle databases from the year 2011 to October 2013. The search terms used to retrieve the information were melatonin, adverse effects of melatonin, consumption of melatonin, and day time consumption of melatonin. The search retrieved approximately 800 publications. These were narrowed down by refining and limiting the search to the adverse effect of daytime melatonin consumption which resulted in more than 90 articles. These articles, in general, relate to therapeutic uses of melatonin. As such these articles would have limited relevance to the safety assessment of food ingredient use and therefore, are not discussed further in this memorandum.

However, there was one relevant article pertaining to a known physiological response to ingested melatonin (Lavoie et al. 2013[1]). This article describes the effect of oral administration of melatonin (90 mg) during daytime in 7 beagle dogs (4 males and 3 females) on the electroretinogram (ERG) in photopic (well-lit) and scotopic (darkness or low-lit) conditions. The ERG is used to assess the circadian changes in the retinal function and allows the direct assessment of the retinal cone and rod system. The a-wave is generated mainly by the photoreceptors whereas the b-wave is generated mostly from the ON-bipolar cells. In this study, the results show that melatonin ingestion during the day decreased the photopic ERG a- and b- wave amplitude dramatically by about 61% and 54% respectively suggesting a significant impact on the retinal cone response. In scotopic ERG, melatonin ingestion had no significant impact on the a- and b-wave amplitude. These results are consistent with similar effects observed in studies in humans and rodents (as previously described in the Melatonin Scientific Memorandum, dated 7/25/11). In

[1] Lavoie J, Rosolen SG, Chalier C, Hébert M. Negative impact of melatonin ingestion on the photopic electroretinogram of dogs. Neurosci Lett. 543:78–83, 2013.

humans, the decrease of the maximal cone response was about 8%, but the dose of melatonin ingested (15 mg) was much lower than the dose used in the dogs. In rats' retinas, melatonin showed cellular toxicity to photoreceptor cells. These results demonstrated that rodents, dogs, and humans reiterate the negative impact of daytime melatonin ingestion on the retinal cone functioning. Moreover, many studies have shown that dopamine produced during the day biases the system in favor of the cones, whereas retinal melatonin produced at night has the opposite effect and promotes activity of the rod system. This cycle shows a 24 h-rhythm with melatonin showing a peak during the dark phase and dopamine being stimulated by light. This result is also consistent with the suggestion that when melatonin is taken during the day, when it is thought to be absent, it acts as an inhibitor of retinal dopamine (not measured in the dog study), and promotes night vision through the decrease in retinal cone functioning. It can be concluded that exogenous melatonin as well as endogenous melatonin play a role in regulating a day and night functional shift in the retina. Inappropriate (i.e., daytime) exposure of the eye to melatonin sends the dark signal even at the level of the retina and promotes night vision, decreases the sensitivity to light, and may lead to ocular toxicity.

Conclusion

As discussed in the "Melatonin Scientific Memorandum," dated July 25, 2011, melatonin is a neurohormone that is tightly regulated and secreted prominently during the night and regulates various circadian activities in many target organs. In addition to the involvement of melatonin in circadian rhythms, the hormone has a variety of physiological and metabolic functions.

Inappropriate use of melatonin causes disruption of circadian rhythms exerts adverse effects on multiple areas of human physiology including the central nervous system, reproductive/developmental system, the retinal photoreceptors, the cardiovascular system, glucose metabolism, immune system as well as carcinogenesis.

Therefore, the exogenous consumption of melatonin as an ingredient in beverages and/or foods cannot be considered safe for the general population. Additionally, in reviewing the recent literature, there is no evidence to suggest otherwise or to contradict the conclusions made in the Melatonin Scientific Memorandum (July 25, 2011), and hence the previous memo is still accurate and valid to use for your current case.