



**Department of Health and Human Services
Food & Drug Administration
21-CFR-Part-111 [Docket No. 95N-0304]**

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Submitted to: Dockets Management Branch (HFA-305),
Food and Drug Administration
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Dietary Supplements Containing Ephedrine Alkaloids; Comments from Circadian Technologies, Inc.

Summary

Circadian Technologies Inc. strongly supports the FDA proposed ruling on June 4th 1997 (62 FR 30678) to amend the regulations to require the label of dietary supplements containing ephedrine alkaloids to bear a clear warning statement about health risks.

In response to the re-opening of this comment period in Docket No. 95N-0304, Circadian Technologies offers evidence to the FDA that ephedrine alkaloids may pose a significant risk of illness or injury to a substantial subgroup of the working population of the United States; the 14.5% of the workforce (approximately 15 million Americans) who work outside the traditional hours of 9am to 5pm ("shiftworkers"). Evidence suggests that members of this population subgroup have a high prevalence of prolonged and regular use of such substances as alertness-enhancing agents, often in combination with the excessive use of caffeine and other drugs.

We also propose a specific addition to the wording of the warning label drafted by the FDA in Docket No. 95N-0304 to include a statement of the significant risk of illness or injury with "prolonged" and or "regular" use of such substances.

Significant health risks of ephedrine alkaloids in shiftworkers

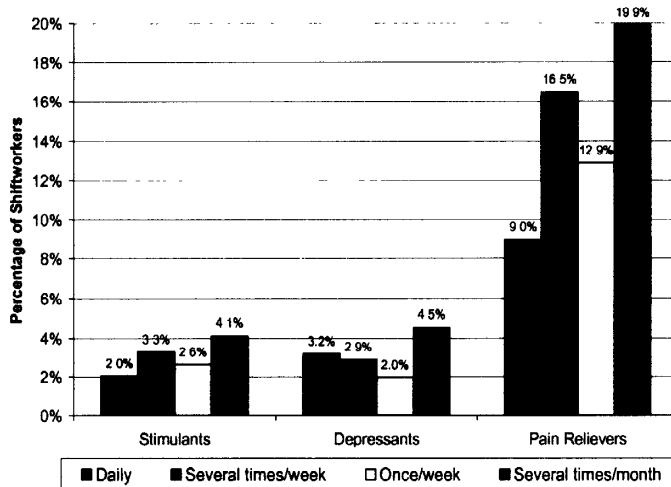
Data from the Bureau of Labor Statistics shows that approximately 17.6% percent of the working population in the United States works outside the traditional hours of 9am to 5pm¹ (23.8 million people). Long work hours or night work can cause significant fatigue due to lack of rest and restorative sleep.

Circadian Technologies Inc. (CTI) has assisted 24/7 companies and their employees to manage the issues of working round-the-clock for more than two decades. At the same time, CTI has gathered the largest databases of health, safety, and work-related data from shiftworkers in the USA. The evidence in this document relates to data from 10,500 shiftworkers collected over the last 5 years (1997 to 2003) from a range of industries across the USA. At this time, the average shiftworker in the USA at this time is 39.6 years old, male, 190 lbs in weight with a body mass index of 27.6. On average, shiftworkers consume 3.15 caffeinated beverages a day, and 8.3 alcoholic beverages a week. Of significant concern is the increased prevalence of stimulant use in this group.

Shiftworkers are known to use stimulatory substances to increase alertness and cope with fatigue at work^{3,4,5,6}. These include legally available substances such as Ephedra, No-Doz,



Vivarin, Yellow-Jackets, and more (which can be found in any convenience store or truck stop), and abuse of regulated substances such as amphetamines. In the *Evidence Report and Technology Assessment of Ephedrine* prepared for the Agency for Healthcare Research and Quality in February 2003², the use of alertness-enhancing agents was discussed in the death of two truck drivers on page 82 and page 83, and a shiftworker on page 85.



By extrapolating our database of 10,500 shiftworkers to the population as a whole, we predict that 2.8 million shiftworking Americans use stimulants such as Ephedra regularly.

According to our databases, 12.1% (2,800,000 people) use stimulants at least several times a month: 2% of shiftworkers use stimulants every day (486,000 people), 3.3% use them "several times a week" (781,000 people), 2.6% use them "once a week" (626,000 people), and 4.1% use them "several times a month" (978,000 people).

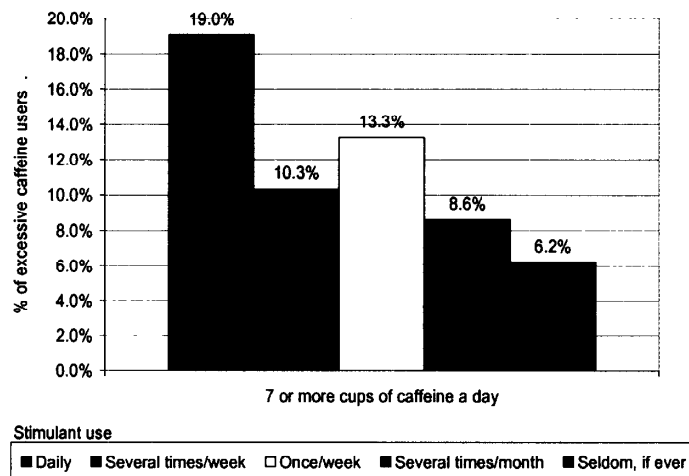
Female shiftworkers use stimulants more regularly than males. Shiftworkers also show increased use of depressants (i.e., Valium, Melatonin, sleeping pills, etc.) and pain relievers that may contain caffeine (i.e., Tylenol, Aspirin, Advil, Motrin, etc.). Approximately, 43% of daily stimulant takers also use daily pain relievers, and 36% of daily stimulant takers also use daily depressants to counter the effects when it comes time to sleep.

More than 69% of shiftworkers are classified as overweight, with 27% presenting body mass indices of 30 or higher; clinically obese. High blood pressure is also common and self-reported in 9.2% of shiftworkers. The shiftwork environment is more likely to involve physical labor, often in higher temperatures than the traditional 9am to 5pm environment, leading to physical stress on the body. It is therefore possible to suggest that the demographics of this population leave them at additional risk of cardiovascular accidents brought on by prolonged or regular use of ephedrine alkaloids.

The greatest concern in reviewing the AHRQ report in February 2003² was the new evidence linking such cardiovascular accidents to the combined use of Ephedrine and caffeine.

Shiftworkers are known to drink caffeinated beverages to ward off fatigue during long overnight shifts. On average, shiftworkers drink 3.15 cups of caffeinated beverage a day.

In those who regularly use stimulants, the prevalence of excessive caffeine use is more than 4 times higher than those who do not use stimulants. Of those who reported daily stimulant use, 19.0% also reported drinking more than 7 cups a day, with nearly half of those reporting the actual figure to be more than 10 cups a day.





The AHQR report concludes that there is “sufficient evidence... that the use of ephedrine .. or ephedrine plus caffeine is associated with 2 to 3 times the risk of .. [health-related issues]”. As such, CTI concludes that dietary supplements containing ephedrine alkaloids present a significant risk of illness or injury to the 1.8 million Americans who work shiftwork and regularly use off-the-shelf herbal stimulants (for purposes other than weight-loss or athletic enhancement) that carry no warning labels.

Warning Statement

CTI strongly supports the FDA proposed ruling to amend the regulations and require the label of dietary supplements containing ephedrine alkaloids to bear a clear warning statement about the health risks of this supplement.

In addition to the statements proposed for the principal display panel (drafted by the FDA in Docket No. 95N-0304) we would recommend that the following statements are added (shown underlined).

WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for pregnant or breast-feeding women or persons under 18. Risk of injury can increase with dose or if used during strenuous exercise, when working irregular, rotating, or extended hours or with other products containing stimulants (including caffeine). Do not use with certain medications or if you have certain health conditions. Stop use and contact a doctor if side effects occur. See more information [...].

References

1. *Current Population Survey*, May 2001. Bureau of Labor Statistics. <ftp://ftp.bls.gov/pub/news.release/History/flex.04182002.news>
2. *Evidence Report and Technology Assessment of Ephedrine*. Agency for Healthcare Research and Quality (AHQR Publication No. 03-E022).
3. Costa G., Apostoli P., d’Andrea G., Gaffuri E. Gastrointestinal and neurotic disorders in textile shiftworkers. In Reinberg A, Vieux N, Andlauer P (eds): *Night and Shift Work: Biological and Social Aspects*. Oxford, Pergamon Press, 1981. Page 215 – 221.
4. Gordon NP, Cleary PD, Parker CE, Czeisler CA. 1986. The prevalence and health impact of shiftwork. *Am. J. Public Health* 76: 1225 – 1228.
5. Tasto DL, Colligan MJ, Skjei EW, Polly SJ. 1978. Health consequences of Shift Work. Cincinnati US Department of Health, Education and Welfare.
6. Lund AK, Presser DF, Mlombereg RD, Williams AF. 1988. Drug use by tractor-trailer drivers. *Journal of Forensic Sci*: 648 – 661.