



Melatonin metabolite excretion among cellular telephone users

J. B. Burch, J. S. Reif, C. W. Noonan, T. Ichinose, A. M. Bachand, T. L. Koleber & M. G. Yost

To cite this article: J. B. Burch, J. S. Reif, C. W. Noonan, T. Ichinose, A. M. Bachand, T. L. Koleber & M. G. Yost (2002) Melatonin metabolite excretion among cellular telephone users, *International Journal of Radiation Biology*, 78:11, 1029-1036, DOI: [10.1080/09553000210166561](https://doi.org/10.1080/09553000210166561)

To link to this article: <https://doi.org/10.1080/09553000210166561>



Published online: 03 Jul 2009.



Submit your article to this journal [↗](#)



Article views: 119



View related articles [↗](#)



Citing articles: 1 View citing articles [↗](#)

Melatonin metabolite excretion among cellular telephone users

J. B. BURCH†*, J. S. REIF†, C. W. NOONAN‡, T. ICHINOSE†, A. M. BACHAND†,
T. L. KOLEBER† and M. G. YOST§

(Received 9 January 2002; accepted 11 June 2002)

Abstract.

Purpose: The relationship between cellular telephone use and excretion of the melatonin metabolite 6-hydroxymelatonin sulfate (6-OHMS) was evaluated in two populations of male electric utility workers (Study 1, $n=149$; Study 2, $n=77$).

Materials and methods: Participants collected urine samples and recorded cellular telephone use over 3 consecutive workdays. Personal 60-Hz magnetic field (MF) and ambient light exposures were characterized on the same days using EMDEX II meters. A repeated measures analysis was used to assess the effects of cellular telephone use, alone and combined with MF exposures, after adjustment for age, participation month and light exposure. **Results:** No change in 6-OHMS excretion was observed among those with daily cellular telephone use >25 min in Study 1 (5 worker-days). Study 2 workers with >25 min cellular telephone use per day (13 worker-days) had lower creatinine-adjusted mean nocturnal 6-OHMS concentrations ($p=0.05$) and overnight 6-OHMS excretion ($p=0.03$) compared with those without cellular telephone use. There was also a linear trend of decreasing mean nocturnal 6-OHMS/creatinine concentrations ($p=0.02$) and overnight 6-OHMS excretion ($p=0.08$) across categories of increasing cellular telephone use. A combined effect of cellular telephone use and occupational 60-Hz MF exposure in reducing 6-OHMS excretion was also observed in Study 2.

Conclusions: Exposure-related reductions in 6-OHMS excretion were observed in Study 2, where daily cellular telephone use of >25 min was more prevalent. Prolonged use of cellular telephones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate the effect.

1. Introduction

The use of cellular or mobile telephones has expanded rapidly in recent years. It is unclear whether exposure to the fields generated by these devices is linked with health effects. Some epidemiologic investigations indicate that cellular telephone exposures may be associated with elevated brain or ocular cancer risks (Hardell *et al.* 1999, 2000, Stang *et al.* 2001), particularly in brain regions closest to

where the cellular telephone was held (Hardell *et al.* 1999, 2000). Others have reported no association between cellular telephone use and brain or other cancer risks (Dreyer *et al.* 1999, Morgan *et al.* 2000, Muscat *et al.* 2000, Inskip *et al.* 2001, Johansen *et al.* 2001). The interpretation of these initial studies is hindered by the relatively short follow-up periods in relation to tumour latency and with difficulties in accurately reconstructing the degree and type of exposure to cellular telephones (Rothman 2000, Frey 2001). Findings from two recent studies add to evidence suggesting that analogue cellular telephone use may be linked with increased brain cancer risks (Hardell *et al.* 2000, 2002, Auvinen *et al.* 2002). In Sweden, analogue cellular telephone use was associated with a brain tumour odds ratio (OR) of 1.3 (95% confidence interval [CI]: 1.02–1.6) (Hardell *et al.* 2002). The OR for acoustic neurinoma was 3.5 (1.8–6.8), whereas no clear association was observed for digital or cordless telephone use (Hardell *et al.* 2002).

Cellular telephone use has also been associated with cognitive and neurological symptoms as well as with altered EEG activity, sleep patterns and neuroendocrine function (Hyland 2000, Krewski *et al.* 2001). Reduced secretion of the hormone melatonin or the excretion of its major urinary metabolite, 6-OHMS, has been reported in some studies of humans exposed to magnetic fields (MFs) (Wilson *et al.* 1990, Pfluger and Minder 1996, Burch *et al.* 1998, 1999, 2000, Karasek *et al.* 1998, Wood *et al.* 1998, Juutilainen *et al.* 2000). Because melatonin has oncostatic (Conti and Maestroni 1995, Panzer and Viljoen 1997, Frascini *et al.* 1998), immune-enhancing (Conti and Maestroni 1995, Frascini *et al.* 1998) and antioxidant properties (Reiter 1998), reduced secretion of this hormone in response to MF exposure has been suggested as a plausible mechanism to explain increased cancer risks in human populations exposed to MFs (Stevens and Davis 1996). Studies of human melatonin production in response to cellular telephone exposures have been limited to small groups of healthy, young, white male subjects in laboratory-based settings using digital

*Author for correspondence;
e-mail: james.burch@colostate.edu

†Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO 80523, USA.

‡Agency for Toxic Substances and Disease Registry, Atlanta, GA 30333, USA.

§Department of Environmental Health, University of Washington, Seattle, WA, USA.

(primarily GSM or Global System for Mobile Communication) rather than analogue cellular telephone exposures (Mann *et al.* 1998, de Seze *et al.* 1999, Radon *et al.* 2001). Melatonin suppression was not observed in these studies although a modest reduction in rapid eye movement (REM) sleep and a transient enhancement of cortisol secretion was observed in the largest study (Mann *et al.* 1998). A lack of 'real-world' exposure conditions (de Seze *et al.* 1999) and a need for larger sample sizes (Mann *et al.* 1998, Radon *et al.* 2001) was acknowledged by the investigators. The effect of analogue cellular telephone use on human melatonin production has not been characterized.

We conducted several epidemiologic studies of human melatonin production in response to 60-Hz MF exposures among electric utility workers (Burch *et al.* 1998, 1999, 2000). Urinary excretion of 6-OHMS, a reliable marker of melatonin production (Bojkowski *et al.* 1987, Aldous and Arendt 1988), was decreased in these workers under certain MF exposure conditions (Burch *et al.* 1998, 1999, 2000). In the group of 142 workers studied during 1995, we found some evidence that cellular telephone use may be associated with decreased 6-OHMS excretion (Burch *et al.* 1997, 1999). However, the effect was not robust, possibly due to the imprecise method of cellular telephone exposure assessment used (Burch *et al.* 1997, 1999). We incorporated a more quantitative assessment of cellular telephone use in subsequent investigations by asking subjects to estimate the number of minutes they used cellular telephones on each day that 6-OHMS determinations were made. Self-reported estimates of current cellular telephone use are reasonably well correlated with cellular telephone billing records (Spearman correlation coefficients = 0.70–0.79) (Funch *et al.* 1996). Here we evaluate whether workplace cellular telephone use in two separate populations of male electric utility workers was associated with decreased 6-OHMS excretion. Workers were provided with cellular telephones by their employers for use on the job. Interviews with utility personnel indicated that analogue cellular telephones were predominantly used in both populations at the time these studies were performed.

2. Materials and methods

The study populations were comprised of 149 (Study 1) and 77 (Study 2) men between the ages of 18 and 60 with at least 1 month of employment in an electric power generation (power plant operators, mechanics, electricians), distribution (linemen, meter readers, substation operators) or utility administra-

tion and maintenance position. Data were collected from nine regional electric utilities between January and September 1997 (Study 1) and between April and June 1998 (Study 2). A different population of workers participated in each study.

The methods used to characterize melatonin production in electric utility workers have been described by Burch *et al.* (2000). Briefly, total overnight and post-work urine samples were collected on 3 consecutive workdays by each participant. Melatonin production was assessed by radioimmunoassay of 6-OHMS (CIDtech, Mississauga, Ontario, Canada). Overnight 6-OHMS excretion and creatinine-adjusted nocturnal (first void) and post-work 6-OHMS concentrations (6-OHMS/cr) were calculated.

Cellular telephone use was assessed by asking participants to record the amount of time spent using a cellular telephone at work on each day of participation. At the end of the 3-day study period, each subject completed a questionnaire covering multiple items potentially related to 6-OHMS excretion or MF exposure. These included personal (e.g. age, height, weight, race, socio-economic status), occupational (e.g. years of work experience, physical activity, work with chemicals, work with electrical tools/equipment), lifestyle (e.g. tobacco, alcohol, caffeine and vitamin consumption, exercise, use of electrical appliances) and medical factors (e.g. consumption of melatonin, antidepressants, tranquilizers, steroid hormones, anti-inflammatory agents, disease history, health status).

Personal exposure to 60-Hz MFs and light was also characterized in Study 1 and 2 subjects. Each participant wore an EMDEX II meter (EnerTech Consultants, Campbell, CA, USA) with an adapted light sensor (Grasby Optronics, Orlando, FL, USA) at the waist, and ambient MF and light exposures were logged at 15-s intervals for 24 h day⁻¹ over the same 3 work days as urine sample collection (Burch *et al.* 1998, 1999, 2000). Work shift time-weighted average magnetic field and light exposures were summarized from the EMDEX recordings on each day.

Statistical analyses were performed with the Proc Mixed procedure for repeated measures in the Statistical Analysis System (SAS Institute, Inc., Cary, NC, USA) computer program using log-transformed values of 6-OHMS variables. The maximum likelihood estimates of cellular telephone use as a fixed effect were calculated for 6-OHMS variables using an unstructured covariance matrix. Subjects were grouped based on the number of minutes of workplace cellular telephone use on each day and least-squares means (adjusted for the effects of age, month of participation and workplace ambient light

exposure) of overnight 6-OHMS excretion and nocturnal or post-work 6-OHMS/cr concentrations were calculated for each group. Least-squares means of the dependent variable are obtained in a multivariate model by holding other covariates in the model to their means (Searle *et al.* 1980). Adjusted mean 6-OHMS levels among workers without cellular telephone use were compared with those with >25 min of use via the least significant differences statistic in SAS. Separate analyses were performed for the Study 1 and 2 populations. Trend tests across categories of cellular telephone use were performed using linear contrasts in Proc Mixed based on coefficients that accounted for unequal cell sizes and uneven intervals between categories of cellular telephone use (Kirk 1982). To evaluate potential effect modification by 60-Hz fields, participants in different cellular telephone use categories were stratified into tertiles of mean workplace MF exposure and adjusted mean 6-OHMS levels in each stratum were compared as described above. In addition, questionnaire items were individually screened for potential associations with the 6-OHMS variables using a cut point of $p < 0.10$. The interpretation of the results did not change when additional confounders selected for nocturnal 6-OHMS/cr (use of chemicals at work, exercise, use of electric bed heaters, electric appliance use, consumption of ibuprofen), overnight 6-OHMS (use of chemicals at work, height, ethnicity, eye colour, computer use, work outdoors, consumption of ibuprofen), and post-work 6-OHMS/cr (body mass index, employer, electric and microwave oven use, use of electric power tools) were included in the analysis.

3. Results

In Study 1, the mean ($\pm$ SD) age of participants was 44 ± 9 years; approximately 91% were Caucasian and non-Hispanic. There were 60 (40%) electric power distribution, 50 (34%) generation, and 39 (26%) administrative and maintenance (comparison) workers. The mean age of the Study 2 workers was 41 ± 8 years and approximately 88% were Caucasian and non-Hispanic. There were 29 (38%) electric power distribution, 22 (29%) generation and 23 (30%) comparison workers (no response, $n = 3$). As expected, there was a clear diurnal variation in 6-OHMS excretion among workers in both populations. Mean nocturnal 6-OHMS/cr levels (Study 1 = $18.2 \text{ ng mg}^{-1} \text{ cr}$; Study 2 = $20.5 \text{ ng mg}^{-1} \text{ cr}$) were approximately six times greater than post-work 6-OHMS cr levels (Study 1 = $3.1 \text{ ng mg}^{-1} \text{ cr}$; Study 2 = $3.5 \text{ ng mg}^{-1} \text{ cr}$). Inspection of covariance parameter estimates for 6-OHMS excretion indicated

that within-subject variability was equal to or less than between-subject variability in both study populations (Littell *et al.* 1998).

The prevalence of cellular telephone use differed among workers in the two studies (figure 1). In Study 1, three subjects reported cellular telephone use of $>25 \text{ min day}^{-1}$ (5 worker-days total). Only one individual was in this category on all 3 days and there was no cellular telephone use $>30 \text{ min day}^{-1}$. No statistically significant difference or trend in adjusted mean 6-OHMS excretion was observed among men with elevated cellular telephone use compared with those without cellular telephone use in Study 1 (table 1). In Study 2, five participants used cellular telephones for $>25 \text{ min day}^{-1}$ (13 worker-days total). Four of the five individuals used a cellular telephone daily for $>25 \text{ min}$. In the Study 2 population, cellular telephone use $>25 \text{ min day}^{-1}$ was associated with lower adjusted mean nocturnal 6-OHMS/cr concentrations ($p = 0.05$) and overnight 6-OHMS excretion ($p = 0.03$) compared with those without cellular telephone use (table 1). The adjusted mean post-work 6-OHMS/cr concentrations were elevated among those with $>25 \text{ min}$ of cellular telephone use compared with those with none, although the difference was not statistically significant ($p = 0.08$, table 1). There was a decreasing trend of adjusted mean nocturnal 6-OHMS/cr concentrations ($p = 0.02$) and overnight 6-OHMS excretion ($p = 0.08$) and an increasing trend of post-work 6-OHMS/cr levels ($p = 0.09$) across categories of increasing cellular telephone use (table 1). Potential cut point bias was evaluated by re-analysing the data using 20 or 30 min of cellular telephone use per day to define the highest exposure group and the results were consistent with those described above (data not shown). Analyses

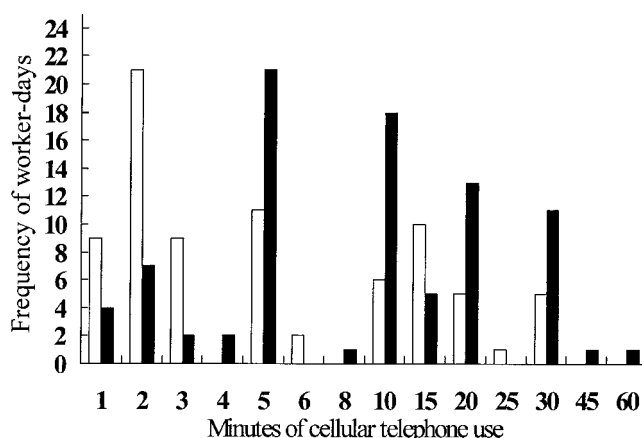


Figure 1. Number of worker-days of participation for different categories of cellular telephone use plotted among participants in Study 1 (1997, white bars) and Study 2 (1998, black bars).

Table 1. Melatonin metabolite excretion^a in cellular telephone users, Colorado, 1997 and 1998.

Categories of cellular phone use at work	<i>n</i> (worker-days) ^b	Mean cellular phone use (min) ^c	Nocturnal 6-OHMS/cr (ng mg ⁻¹ cr)	Overnight 6-OHMS (μg)	Post-work 6-OHMS/cr (ng mg ⁻¹ cr)
Study 1, 1997					
0 min	314	0	15.0 ± 1.1	8.2 ± 1.1	2.3 ± 1.1
1–10 min	71	5 ± 4	14.3 ± 1.1	7.3 ± 1.1	1.8 ± 1.1
11–25 min	14	18 ± 3	14.9 ± 1.2	8.6 ± 1.2	3.1 ± 1.2
>25 min	5	30 ± 0	14.0 ± 1.4	7.3 ± 1.5	3.1 ± 1.5
Difference (%): 0 versus >25	—	—	—7	—11	+35
Two-tailed <i>p</i> : 0 versus >25	—	—	0.83	0.75	0.50
Linear trend test <i>p</i>	—	—	0.73	0.63	0.68
Study 2, 1998					
0 min	137	0	18.9 ± 1.1	9.8 ± 1.1	2.6 ± 1.1
1–10 min	54	6 ± 3	16.4 ± 1.1	10.3 ± 1.1	2.7 ± 1.1
11–25 min	15	18 ± 2	15.5 ± 1.2	10.0 ± 1.2	2.8 ± 1.2
>25 min	13	34 ± 9	12.5 ± 1.2	6.5 ± 1.2	3.9 ± 1.2
Difference (%): 0 versus >25	—	—	—34	—34	+50
Two-tailed <i>p</i> : 0 versus >25	—	—	0.05	0.03	0.08
Linear trend test <i>p</i>	—	—	0.02	0.08	0.09

^aLeast-squares means (±SEM) adjusted for age, light exposure at work, month of participation.

^bAverage number of workers in each category can be obtained dividing worker-days by 3.

^cArithmetic mean (±SD).

were also performed among Study 2 participants for each day of participation separately. There were no statistically significant differences in mean nocturnal 6-OHMS excretion on the first and second participation days and no differences in post-work 6-OHMS levels on any given day (data not shown). On the third day of participation, Study 2 participants with >25 min of cellular telephone use had lower adjusted mean nocturnal 6-OHMS/cr concentrations (12.7 ng mg⁻¹ cr, *p*=0.02 versus no use category) and overnight 6-OHMS excretion (6.5 μg, *p*=0.01 versus no use category) compared with those with 11–25 min (22.0 ng mg⁻¹ cr and 13.0 μg, respectively), 1–10 min (17.2 ng mg⁻¹ cr and 10.6 μg, respectively) or no cellular telephone use (21.3 ng mg⁻¹ cr and 10.8 μg, respectively).

In Study 1, the numbers of workers in the highest exposure categories were inadequate to evaluate the combined effects of cellular telephone and 60-Hz MF exposures on 6-OHMS excretion. For the Study 2 population, adjusted mean 6-OHMS excretion resulting from a combination of cellular telephone and occupational 60-Hz MF exposure is presented in table 2. No differences were found in the mean nocturnal 6-OHMS excretion across categories of cellular telephone use for subjects in the low and intermediate tertiles of workplace 60-Hz MF exposure. However, workers in the highest category of cellular telephone use who were also in the highest tertile of workplace 60-Hz MF exposure had lower mean nocturnal 6-OHMS/cr concentrations (*p*=

0.01) and overnight 6-OHMS excretion (*p*=0.04) compared with those with higher cellular telephone use but low 60-Hz MF exposure (table 2, row comparison). Similarly, among workers in the highest tertile of workplace MF exposure, those with higher cellular telephone use had lower mean nocturnal 6-OHMS/cr concentrations (*p*<0.01) and overnight 6-OHMS excretion (*p*=0.02) compared with those with no cellular telephone use (table 2, column comparison). The adjusted mean post-work 6-OHMS levels did not differ appreciably across the different categories of cellular telephone use and workplace 60-Hz MF exposure. Also, there was no evidence of elevated mean 60-Hz MF exposures among those with elevated cellular telephone use (data not shown).

4. Discussion

To our knowledge, these were the first epidemiological studies to evaluate the potential effect of cellular telephone use on human melatonin production under 'real life' conditions. Two separate populations of electric utility workers were evaluated using a repeated measures design. In Study 1, statistical power was limited. Multiday cellular telephone use >25 min day⁻¹ was only observed in one worker. In Study 2, mean nocturnal 6-OHMS levels were lower in workers with a daily cellular telephone use >25 min, and tests for trend supported these observations. Four of these five workers reported 3 consecutive days of cellular telephone use of >25 min and

Table 2. Melatonin metabolite excretion^a in cellular phone users stratified by mean workplace magnetic field exposure, Colorado, 1998.

Categories of cellular phone use at work	Workplace arithmetic mean exposure tertiles ^b			Two-tailed <i>p</i> : 1 versus 3
	1 (0.5 ± 0.2 mG)	2 (1.1 ± 0.2 mG)	3 (5.0 ± 8.3 mG)	
Nocturnal 6-OHMS/cr (ng mg ⁻¹ cr)				
0 min	16.7 ± 1.1 (<i>n</i> = 38)	19.3 ± 1.1 (49)	20.6 ± 1.1 (50)	0.08
1–10 min	17.5 ± 1.1 (26)	15.1 ± 1.1 (14)	16.5 ± 1.2 (14)	0.75
> 10 min	17.3 ± 1.3 (5)	18.2 ± 1.2 (13)	7.8 ± 1.2 (10)	0.01
Two-tailed <i>p</i> : 0 versus > 10 min	0.90	0.74	< 0.01	
Overnight 6-OHMS (μg)				
0 min	10.3 ± 1.1 (<i>n</i> = 38)	10.5 ± 1.1 (49)	8.8 ± 1.1 (50)	0.18
1–10 min	10.0 ± 1.1 (26)	10.1 ± 1.1 (14)	10.5 ± 1.1 (14)	0.77
> 10 min	9.3 ± 1.2 (5)	11.0 ± 1.2 (13)	5.6 ± 1.2 (10)	0.04
Two-tailed <i>p</i> : 0 versus > 10 min	0.65	0.78	0.02	
Post-work 6-OHMS/cr (ng mg ⁻¹ cr)				
0 min	2.6 ± 1.1 (<i>n</i> = 38)	2.7 ± 1.1 (49)	2.6 ± 1.1 (50)	0.99
1–10 min	2.7 ± 1.1 (26)	2.8 ± 1.2 (14)	2.7 ± 1.2 (14)	0.96
> 10 min	2.6 ± 1.4 (5)	3.1 ± 1.2 (13)	3.8 ± 1.2 (10)	0.31
Two-tailed <i>p</i> : 0 versus > 10 min	0.99	0.46	0.10	

^aLeast-squares means ± SEM adjusted for age, light exposure at work, and month of participation (number of worker-days exposure in parentheses). The average number of workers in each category can be obtained by dividing worker-days by 3.

^bTime-weighted arithmetic mean work shift 60-Hz magnetic field exposure (± SD) in parentheses.

reductions in adjusted mean 6-OHMS levels occurred on the third day of participation. The results suggest that a minimum daily and/or a multi-day threshold of cellular telephone use may be necessary to reduce 6-OHMS excretion.

Uncertainties about RF exposures and the small proportion of workers with extensive cellular telephone use limit the interpretation of our results. The dose of non-ionizing radiation received by a cellular telephone user depends on the duration of telephone use and on the type of telephone, the power output, the hand placement, the system traffic and the management software used, and the distance to a cellular telephone tower (ICNIRP 1996, Hyland 2000, Krewski *et al.* 2001). The power output of analogue cellular telephones is greater than that of digital telephones. However, it is possible that subjects with high daily cellular telephone use preferred digital telephones because of their longer battery life. Also, non-work cellular telephone use was not determined in our studies, although personal (off-duty) cellular telephone use is not expected to have been highly

prevalent in 1997 and 1998 when these studies were performed.

An increase in adjusted mean post-work 6-OHMS/cr levels among workers with cellular telephone use > 25 min was observed in both studies, although neither finding was statistically significant. These results were not consistent with our previous findings (Burch *et al.* 1997, 1999), making it difficult to draw conclusions about post-work 6-OHMS/cr excretion and cellular telephone use. The finding that cellular telephone use during work was associated with a reduction in 6-OHMS excretion occurring later that night is consistent with previously observed decreases in nocturnal 6-OHMS excretion following residential and/or workplace exposure to power frequency MFs earlier in the day (Karasek *et al.* 1998, Burch *et al.* 1998, 2000, Juutilainen *et al.* 2000).

The population sizes in our studies were approximately three to 10 times greater than prior laboratory-based studies of human melatonin production in response to cellular telephone exposure. In addition

to sample size differences, digital (modulated, primarily GSM) cellular telephone exposures were previously studied, whereas our studies evaluated predominantly analogue (unmodulated) cellular telephone use. Continuous-wave irradiation may elicit different biological effects than modulated RF exposures (ICNIRP 1996, Krewski *et al.* 2001). Some suggest that modulated cellular telephone fields may be more biologically active than unmodulated exposures (Litovitz *et al.* 1993, Penafiel *et al.* 1997). However, results from two recent studies suggest that analogue cellular telephone use may be more strongly linked with increased central nervous system cancer risks than digital telephones (Auvinen *et al.* 2002, Hardell *et al.* 2002).

The greatest reductions in mean nocturnal 6-OHMS excretion occurred among Study 2 participants whose daily cellular telephone use and workplace MF exposures were both elevated. This could be due to a threshold phenomenon or indicate that RF fields generated by cellular telephones and power frequency (60 Hz) MFs operate through the same biological mechanism in suppressing 6-OHMS excretion. Prior studies of human melatonin production following cellular telephone exposures did not evaluate participant's personal exposure to other RF sources, 60-Hz fields or ambient light (Mann *et al.* 1998, de Seze *et al.* 1999, Radon *et al.* 2001). Consequently, there were no analyses to determine whether such exposures may have influenced the relationship between cellular telephone use and melatonin production.

The potential health consequences of reduced melatonin production in response to cellular telephone or other MF exposures remain to be determined. Extremely low melatonin levels have been observed in otherwise normal healthy individuals (Claustrat 1990). However, there has been no systematic investigation to determine whether people with low endogenous melatonin levels have increased disease risks. The antioxidant properties of melatonin may prevent oxidative DNA damage in numerous organs including the brain, thereby exerting a protective effect against certain disease processes including carcinogenesis (Panzer and Viljoen 1997, Reiter 1998). Circulating melatonin contributes significantly to serum antioxidant capacity in humans (Benot *et al.* 1999) as well as in rodents (Benot *et al.* 1998). Lai and Singh (1997) reported that DNA damage induced in rat brain *in vivo* by exposure to a 2450-MHz field (specific absorption rates 0.6 and 1.2 W kg⁻¹) was ameliorated by pretreatment with melatonin or another antioxidant. Because melatonin is present in the human eye (Martin *et al.* 1992) and inhibits the proliferation of uveal melanoma cells (Hu *et al.* 1998),

it has been suggested that an increased incidence of human uveal melanoma in cellular telephone users may have been mediated by RF-induced melatonin suppression (Stang *et al.* 2001).

5. Conclusions

An evaluation of workplace cellular telephone use on human melatonin production was performed in two populations of electric utility workers where analogue telephones were predominantly used. An exposure-related reduction in 6-OHMS excretion was observed in Study 2, where cellular telephone use >25 min day⁻¹ was more prevalent than in Study 1. A combined effect of cellular telephone use and occupational MF exposure in suppressing 6-OHMS excretion was also evident in Study 2. Future epidemiological and laboratory-based studies assessing the relationship between cellular telephone use and human melatonin production should incorporate 24-h personal assessment of RF/60 Hz fields and ambient light exposures into the study design. In addition, research is needed to determine whether melatonin suppression is linked with adverse health outcomes, including those potentially associated with different types of cellular telephones, or with other forms of RF, 60 Hz or mixed non-ionizing radiation exposures.

Acknowledgements

The authors gratefully acknowledge the cooperation of the participating utilities. Urinary 6-OHMS assays were performed under the direction of Dr Terry Nett, Director of the Radioimmunoassay Laboratory for the CSU Animal Research and Biotechnology Laboratories. The authors thank Ms Jeanette Haddock for assistance with data collection; Ms Xiaoming Sha for assistance with the 6-OHMS assay; and Drs Lee Wilke and Martin Fettman for assistance with the creatinine assays. Dr Scott Davis of the Fred Hutchinson Cancer Research Center provided the design for adaptation of the light sensors to the EMDEX meters. Battelle Pacific Northwest Laboratories and Platte River Power Authority provided light meters. Mr Ken Webster provided computer-programming assistance. This work was supported by research Grant No. 1 R01ES08117 from the National Institute of Environmental Health Sciences, National Institute of Health, USA.

References

- ALDOUS, M. E. and ARENDT, J., 1988, Radioimmunoassay for 6-sulphatoxymelatonin in urine using an iodinated tracer. *Annals of Clinical Biochemistry*, **25**, 298–303.

- AUVINEN, A., HEITANEN, M., LUUKKONEN, R. and KOSKELA, R. S., 2002, Brain tumors and salivary gland cancers among cellular telephone users. *Epidemiology*, **13**, 356–359.
- BENOT, S., GOBERNA, R., REITER, R. J., GARCIA-MAURINO, S. and GUERRERO, J. M., 1999, Physiological levels of melatonin contribute to the antioxidant capacity of human serum. *Journal of Pineal Research*, **27**, 59–64.
- BENOT, S., MOLINERO, P., SOUTTO, M., GOBERNA, R. and GUERRERO, J. M., 1998, Circadian variations in the rat serum total antioxidant status: correlation with melatonin levels. *Journal of Pineal Research*, **25**, 1–4.
- BOJKOWSKI, C. J., ARENDT, J. A., SHIH, M. C. and MARKEY, S. P., 1987, Melatonin secretion in humans assessed by measuring its metabolite, 6-sulfatoxymelatonin. *Clinical Chemistry*, **33**, 1343–1348.
- BURCH, J. B., REIF, J. S., NOONAN, C. W. and YOST, M. G., 2000, Melatonin metabolite levels in workers exposed to 60 Hz magnetic fields: work in substations and with 3-phase conductors. *Journal of Occupational and Environmental Medicine*, **42**, 136–142.
- BURCH, J. B., REIF, J. S., PITRAT, C. A., KEEFE, T. J. and YOST, M. G., 1997, Cellular telephone use and excretion of a urinary melatonin metabolite (abst). In Annual Review of Research on the Biological Effects of Electric and Magnetic Fields from the Generation, Delivery and Use of Electricity. US Department of Energy, November, San Diego, CA.
- BURCH, J. B., REIF, J. S., YOST, M. G., KEEFE, T. J. and PITRAT, C. A., 1998, Nocturnal excretion of a urinary melatonin metabolite in electric utility workers. *Scandinavian Journal of Work, Environment and Health*, **24**, 183–189.
- BURCH, J. B., REIF, J. S., YOST, M. G., KEEFE, T. J. and PITRAT, C. A., 1999, Reduced excretion of a melatonin metabolite in workers exposed to 60 Hz magnetic fields. *American Journal of Epidemiology*, **150**, 27–36.
- CLAUSTRAT, B., BRUN, J. and CHAZOT, G., 1990, Melatonin in humans: neuro-endocrinological and pharmacological aspects. *International Journal of Radiation Applications and Instrumentation—Part B, Nuclear Medicine and Biology*, **17**, 625–632.
- CONTI, A. and MAESTRONI, G. J. M., 1995, The clinical neuroimmunotherapeutic role of melatonin in oncology. *Journal of Pineal Research*, **9**, 103–110.
- DE SEZE, R., AYOUB, J., PERAY, P., MIRO, L. and TOUITOU, Y., 1999, Evaluation in humans of the effects of radiocellular telephones on the circadian patterns of melatonin secretion, a chronobiological rhythm marker. *Journal of Pineal Research*, **27**, 237–242.
- DREYER, N. A., LOUGHLIN, J. E. and ROTHMAN, K. J., 1999, Cause-specific mortality in cellular phone users. *Journal of the American Medical Association*, **282**, 1814–1816.
- FRASCHINI, F., DEMARTINI, G., ESPOSTI, D. and SCAGLIONE, F., 1998, Melatonin involvement in immunity and cancer. *Biological Signals Receptor*, **7**, 61–72.
- FREY, A. H., 2001, Cellular telephones and brain cancer: current research. *Environmental Health Perspectives*, **109**, A200.
- FUNCH, D. P., ROTHMAN, K. J., LOUGHLIN, J. E. and DREYER, N. A., 1996, Utility of telephone company records for epidemiologic studies of cellular telephones. *Epidemiology*, **7**, 229–302.
- HARDELL, L., HALLQUIST, A., MILD, K. H., CARLBERG, M., PAHLSON, A. and LILJA, A., 2002, Cellular and cordless telephones and the risk for brain tumors. *European Journal of Cancer Prevention*, **11**, 377–386.
- HARDELL, L., NASMAN, A., PAHLSON, A. and HALLQUIST, A., 4 May 2000, Case-control study on radiology work, medical X-ray investigations, and use of cellular telephones as risk factors for brain tumors. *Medscape General Medicine*. Available at: [http://www.medscape.com / Medscape / GeneralMedicine / journal / 2000 / v02.n03 mg⁻¹m0504.hard mg⁻¹m0504.hard.html].
- HARDELL, L., NASMAN, A., PAHLSON, A., HALLQUIST, A. and MILD, K. H., 1999, Use of cellular telephones and the risk for brain tumours: a case-control study. *International Journal of Oncology*, **15**, 113–116.
- HU, D. N., MCCORMICK, S. A. and ROBERTS, J. E., 1998, Effects of melatonin, its precursors and derivatives on the growth of cultured human uveal melanoma cells. *Melanoma Research*, **8**, 205–210.
- HYLAND, G. J., 2000, Physics and biology of mobile telephony. *Lancet*, **356**, 1833–1836.
- INSKIP, P. D., TARONE, R. E., HATCH, E. E., WILCOSKY, T. C., SHAPIRO, W. R., SELKER, R. G., FINE, H. A., BLACK, P. M., LOEFFLER, J. S. and LINET, M. S., 2001, Cellular telephone use and brain tumors. *New England Journal of Medicine*, **344**, 79–86.
- INTERNATIONAL COMMISSION ON NON-IONIZING RADIATION PROTECTION (ICNIRP), 1996, Health issues related to the use of hand-held radiotelephones and base transmitters. *Health Physics*, **70**, 587–593.
- JOHANSEN, C., BOICE, J., JR, MCCLAUGHLIN, J. and OLSEN, J., 2001, Cellular telephones and cancer—a nationwide cohort study in Denmark. *Journal of the National Cancer Institute*, **93**, 203–207.
- JUUTILAINEN, J., STEVENS, R. G., ANDERSON, L. E., HANSEN, N. H., KILPELAINEN, M., KUMLIN, T., LAITINEN, J. T., SOBEL, E. and WILSON, B. W., 2000, Nocturnal 6-hydroxymelatonin sulfate excretion in female workers exposed to magnetic fields. *Journal of Pineal Research*, **28**, 97–104.
- KARASEK, M., WOLDANSKA-OKONSKA, M., CZERNICKI, J., ZYLINSKA, K. and SWIETOSLAWSKI, J., 1998, Chronic exposure to 2.9 mT, 40 Hz magnetic field reduces melatonin concentrations in humans. *Journal of Pineal Research*, **25**, 240–244.
- KIRK, R. E., 1982, *Experimental Design*. 2nd edn (Belmont: Brooks/Cole).
- KREWSKI, D., BYUS, C. V., GLICKMAN, B. W., LOTZ, W. G., MANDEVILLE, R., MCBRIDE, M. L., PRATO, F. S. and WEAVER, D. F., 2001, Potential health risks of radiofrequency fields from wireless telecommunication devices. *Journal of Toxicology and Environmental Health, Part B*, **4**, 1–143.
- LAI, H. and SINGH, N. P., 1997, Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. *Bioelectromagnetics*, **18**, 446–454.
- LITOVITZ, T., KRAUSE, D., PENAFIEL, L. M., ELSON, E. C. and MULLINS, J. M., 1993, The role of coherence time in the effect of microwaves on ornithine decarboxylase activity. *Bioelectromagnetics*, **14**, 395–403.
- LITTELL, R. C., HENRY, P. R. and AMMERMAN, C. B., 1998, Statistical analyses of repeated measures data using SAS procedures. *Journal of Animal Sciences*, **76**, 1216–1231.
- MANN, K., WAGNER, P., BRUNN, G., HASSAN, F., HIEMKE, C. and ROSCHKE, J., 1998, Effects of pulsed high-frequency electromagnetic fields on the neuroendocrine system. *Clinical Neuroendocrinology*, **67**, 139–144.
- MARTIN, X. D., MALINA, H. Z., BRENNAN, M. C., HENDRICKSON, P. H. and LICHTER, P. R., 1992, The ciliary body: the

- third organ found to synthesize the indoleamines in humans. *European Journal of Ophthalmology*, **2**, 67–72.
- MORGAN, R. W., KELSH, M. A., ZHAO, K., EXUZIDES, A., HERINGER, S. and NEGRETE, W., 2000, Radiofrequency exposure and mortality from cancer of the brain and lymphatic/hematopoietic systems. *Epidemiology*, **11**, 118–127.
- MUSCAT, J. E., MALKIN, M. G., THOMPSON, S., SHORE, R. E., STELLMAN, S. D., MCCREE, D., NEUGUT, A. I. and WYNDER, E. L., 2000, Handheld cellular telephone use and risk of brain cancer. *Journal of the American Medical Association*, **284**, 3001–3007.
- PANZER, A. and VILJOEN, M., 1997, The validity of melatonin as an oncostatic agent. *Journal of Pineal Research*, **22**, 184–202.
- PENAFIEL, L. M., LITOVITZ, T., KRAUSE, D., DESTA, A. and MULLINS, J. M., 1997, Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells. *Bioelectromagnetics*, **18**, 132–141.
- PFLUGER, D. H. and MINDER, C. E., 1996, Effects of exposure to 16.7 Hz magnetic fields on urinary 6-hydroxymelatonin sulfate excretion of Swiss railway workers. *Journal of Pineal Research*, **21**, 91–100.
- RADON, K., PARERA, D., ROSE, D. M., JUNG, D. and VOLLRATH, L., 2001, No effects of pulsed radio frequency electromagnetic fields on melatonin, cortisol, and selected markers of the immune system in man. *Bioelectromagnetics*, **22**, 280–287.
- REITER, R. J., 1998, Oxidative damage in the central nervous system: protection by melatonin. *Progress in Neurobiology*, **56**, 359–438.
- ROTHMAN, K. J., 2000, Epidemiological evidence on health risks of cellular telephones. *Lancet*, **356**, 1837–1840.
- SEARLE, S. R., SPEED, F. M. and MILLIKEN, G. A., 1980, Populations marginal means in the linear model: an alternative to least squares means. *American Statistician*, **34**, 216–221.
- STANG, A., ANASTASSIOU, G., AHRENS, W., BROMEN, K., BORNFIELD, N. and JOCKEL, K. H., 2001, The possible role of radiofrequency radiation in the development of uveal melanoma. *Epidemiology*, **12**, 7–12.
- STEVENS, R. G. and DAVIS, S., 1996, The melatonin hypothesis: electric power and breast cancer. *Environmental Health Perspectives*, **104**, 135–140.
- WILSON, B. W., WRIGHT, C. W., MORRIS, J. E., BUSCHBOM, R. L., BROWN, D. P., MILLER, D. L., SOMMERS-FLANNIGAN, R. and ANDERSON, L. E., 1990, Evidence for an effect of ELF electromagnetic fields on human pineal gland function. *Journal of Pineal Research*, **9**, 259–269.
- WOOD, A. W., ARMSTRONG, S. M., SAIT, M. L., DEVINE, L. and MARTIN, M. J., 1998, Changes in human plasma melatonin profiles in response to 50 Hz magnetic field exposure. *Journal of Pineal Research*, **25**, 116–127.