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Oxidative DNA damage estimated by urinary 8-hydroxydeoxyguanosine and indoor air pollution among non-smoking office employees

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Abstract

This study investigated whether urinary 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of oxidative stress, was associated with indoor air quality for non-smokers in high-rise building offices. With informed consents, urine samples from 344 non-smoking employees in 86 offices were collected to determine 8-OHdG concentrations. The concentrations of carbon dioxide (CO_2) and total volatile organic compounds (TVOCs) in each office and outside of the building were simultaneously measured for eight office hours. The average workday difference between indoor and outdoor CO_2 concentrations (dCO_2) was used as a surrogate measure of the ventilation efficiency for each office unit. The CO_2 levels in the offices ranged 467–2810 ppm with a mean of 1170 ppm, or 2.7 times higher than that in the outside air. The average urinary 8-OHdG levels among employees increased from 3.10 μg/g creatinine, for those at the lowest tertile levels of both dCO_2 and TVOCs, to 6.27 μg/g creatinine, for those at the highest tertile levels. Multivariate logistic regression analysis showed that the risk of having the urinary 8-OHdG level of greater than the median, 4.53 μg/g creatinine, for participants was increased significantly at the highest tertile dCO_2 level of >680 ppm (odds ratio (OR) = 3.37, 95% confidence interval (CI) = 1.20–9.46). The effect was significant at the middle tertile TVOCs level of 114–360 ppb (OR = 2.62, 95% CI = 1.43–4.79), but not at the highest tertile. Inadequate ventilation in office increases the risk of building-related oxidative stress in non-smoking employees.

Keywords: Oxidative stress; 8-hydroxydeoxyguanosine; Carbon dioxide; Volatile organic compounds; Ventilation rate; High-rise building office

1. Introduction

Reactive oxygen species (ROS) in urban air pollutants may conduce to DNA damage (Chuang et al., 2003; Staessen et al., 2001; Vine et al., 2000). In the exposure of ROS, 8-hydroxydeoxyguanosine (8-OHdG) is formed by the action of hydroxyl radicals on the C-8 of guanosine as a marker of repairing damaged DNA (Floyd et al., 1990; Fraga et al., 1990; Shigenaga et al., 1989). Calderon-Garciduenas et al. (1999) found that 8-OHdG levels in the nasal cavity respiratory track epidermal cells is higher in children living in the urban area, compared to rural areas, and attributed it to air pollution.

Elevated urinary 8-OHdG levels have also been detected in smokers and occupational drivers, due to the formation of oxidative DNA adduct from routine exposure to cigarette smoke and traffic exhaust (Anderson et al., 1991; Chuang et al., 2003; Loft et al., 1992; Samet et al., 1987). Lodovici et al. (2000) found the average of urinary 8-OHdG concentrations in smokers was 2-fold higher than that in never smokers. Chuang et al. (2003) found the distribution of urinary 8-OHdG levels in community male

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smokers is similar to that in male never smoking taxi drivers. These findings suggest a considerable contribution of occupational driving to the level of 8-OHdG.

Tobacco smoke may stimulate the activation of the macrophage cells in the human body, leading to oxidative damage in the respiratory track (Anderson et al., 1991; Samet et al., 1987). In addition to chemicals in automobile exhaust and tobacco smoke, volatile organic carbons (VOCs) and ionization radiation can also result in a rise of urinary 8-OHdG levels (Carstensen et al., 1999; Tagesson et al., 1995, 1996; Wilson et al., 1993).

Most of the above studies are related to exposure in industries, traffic and tobacco smoke. To our knowledge, no study has investigated the contribution of indoor air pollution to the urinary 8-OHdG levels for office employees who have less exposure to traffic exhaust and tobacco smoking. This study evaluated the association between the levels of urinary 8-OHdG and indoor air pollution exposure for non-smoking individuals working in high-rise building offices.

2. Materials and methods

2.1. Study subjects and data collection

From November 2003 through June 2004, we randomly selected 16 government and commercial organizations in eight high-rise buildings with central ventilation system, in Taipei city, Taiwan, for subject recruitment and indoor air pollutants measurement. Five organizations declined to participate. Three of the remaining 11 institutions were excluded from this study because urinary specimens were not available. None of these office buildings previously reported indoor air quality issues. An invitation letter explaining the study was delivered to potential participants in 86 office units in the remaining eight organizations. With informed consent, 398 persons with full time jobs at these offices responded to our invitation (response rate 61.7%). Data of smokers were excluded from the present study. Each person was asked to provide a spot urine sample and return a self-reported questionnaire with information on lifestyle, and socioeconomic and health status. Urine samples, collected from participants at the end of the work day, were transported in a cold box of 4 °C to the laboratory stored at −80 °C until analysis. A review committee established at the National Science Council, Taiwan, reviewed and approved this study. We have adhered to the study ethics.

2.2. dCO_2 and TVOCs measurement

We used portable monitors at each office to simultaneously detect the levels of carbon dioxide (CO_2) and total volatile organic compounds (TVOCs) to represent indoor air pollution levels. The CO_2 measure was standardized against a wide range (0–5000 ppm) of CO_2 and delicate resolution (1 ppm) (Q-TRAK IAQ Model 8551, TSI Incorporated, Shoreview, MN, USA). TVOCs measures were standardized against 102 categories of volatile organic compounds (VOCs) with acceptable deviation (20 ppb) (PGM-7240, RAE SYSTEMS, California, USA). During office hours (from 9:00 a.m. to 6:00 p.m.), monitors were placed in the middle of the office, at 1.2 m height, away from any window or air-conditioner. Standard gas calibration was performed prior to each measurement. Eight-hour averaged workday difference between indoor and outdoor CO_2 concentrations ($dCO_2 = CO_{2\ indoor} - CO_{2\ outdoor}$) (Apte et al., 2000) was used as a surrogate measure for building occupancy and per-person ventilation in an office.

2.3. Determinations of urinary creatinie and 8-OHdG

Thawed urine samples were pretreated with centrifuge at 3000g for 10 min to remove the particulate matters. The creatinine value in the urine sample was determined with an automatic analyzer (Hitachi 7250, Tokyo, Japan) based on the Jaffe colorimeter reaction (Nerurkar and Sahasrabudhe, 1960).

Urinary 8-OHdG was determined using the OXIS research^{TM} enzyme-linked immunosorbent assay (ELISA) kit (Japan Institute for the Control of Aging, Shizuoka, Japan) with high sensitivity and specificity and easy operation. At room temperature, 50 μl of primary antibody were added to 50 μl aliquot of each sample or standard in microtiter plates pre-coated with 8-OHdG for assay, using the procedure developed by Yin et al. (1995). The 8-OHdG concentrations in samples were determined by comparing the absorbance values at 450 nm with a calibration curve generated by 0.5, 2, 8, 20, 80 and 200 ng/ml 8-OHdG. The results were expressed as μg/g creatinine.

2.4. Statistical analysis

Means ± standard deviations, medians and ranges for both indoor and outdoor CO_2, and TVOCs concentrations were calculated. Student's t-test and generalized linear model (GLM) were performed to evaluate the differences of urinary 8-OHdG levels by sex and age, respectively. We further performed comparisons in urinary 8-OHdG levels to determine the interaction between exposures to CO_2 and VOCs. Means of urinary 8-OHdG contents were calculated by tertiles of dCO_2 (<390 ppm, 390–680 ppm and >680 ppm) and tertiles of TVOCs (<114 ppb, 114–360 ppb and >360 ppb). Using the overall median of 8-OHdG levels as the cut-off of elevated concentration, odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated using logistic regression analyses to identify factors associated with the elevation of urinary 8-OHdG, such as gender, age, working hours per day, using sanitizing chemicals, environmental tobacco smoking (ETS) sensitivity, chemical sensitivity, exposure to ETS, and indoor environmental quality. The overall median 8-OHdG (4.53 μg/g creatinine) among all study participants was used as the cut-off point of elevated concentration in the logistic regression analysis.

3. Results

3.1. Levels of dCO_2 and TVOCs exposure

Table 1 depicts the statistical distribution of environmental measurements for all 86 offices. The results of 8-hour measures of indoor air revealed an hourly average (standard deviation, SD) difference of CO_2 (dCO_2)

Table 1
Summary statistics for environmental measurements among high-rise building offices with study participants worked in

Index	Mean	S.D.	Range
Environmental covariates ($n = 86$)			
$CO_{2indoor}$ (100 ppm)	11.7	6.06	4.67–28.1
$CO_{2outdoor}$ (100 ppm)	4.35	0.60	3.37–5.63
Difference[a]	7.36	6.29	−0.96–23.9
$TVOC_{indoor}$ (100 ppb)	12.1	60.9	0.06–557
$TVOC_{outdoor}$ (100 ppb)	1.81	1.60	0.05–4.25
Difference[a]	10.3	60.5	−1.46–553
Relative humidity, RH (%)	57.6	7.36	45.5–79.7
Temperature, T (°C)	23.6	1.68	18.6–28.4

[a]Between indoor and outdoor.

concentrations of 736 (629) ppm, between indoor and outdoor measures, with the range between −96 and 2390 ppm. The hourly average (SD) TVOCs concentration was 1210 (6090) ppb with the range between 6 and 55,700 ppb in the offices.

3.2. Urinary 8-OHdG levels in never smokers

The daily average (SD) and median time they exposed to the office environments was 8.6 (1.4) and 9.0 h, respectively, with the range between 3 and16 h (data not shown). Most participants were women (81.4%) and aged between 30 and 39 years old (40.1%) (Table 2). The overall average (SD) urinary 8-OhdG in the whole samples was 5.15 (2.86) μg/g creatinine with a median of 4.53 μg/g creatinine. The average was somewhat greater in men (5.43 ± 2.65 μg/g creatinine) than in women (5.08 ± 2.91 μg/g creatinine) ($P = 0.38$), and higher in participants of 30–39 years old (5.44 ± 3.12 μg/g creatinine) than in other age groups ($P = 0.43$).

Table 2
Averages and ranges of urinary 8-hydroxydeoxyguanosine levels measured for non-smoking office employees by sex and environmental tobacco smoke exposure

Variable (*N*)	8-OHdG[a] (μg/g creatinine)			*P*-value
	Mean (S.D.)[b]	Median	Range	
All (344)	5.15 (2.86)	4.53	1.06–16.7	
Sex				
Female (280)	5.08 (2.91)	4.48	1.06–16.7	0.38[c]
Male (64)	5.43 (2.65)	4.89	1.06–12.1	
Age				
<30 (95)	5.04 (2.45)	4.51	1.07–12.09	0.43[d]
30–39 (138)	5.44 (3.12)	4.84	1.08–16.66	
40–49 (54)	4.75 (2.66)	4.05	1.06–11.28	
>50 (57)	4.99 (3.02)	4.95	1.06–11.82	

[a]8-hydroxydeoxyguanosine.
[b]Standard deviation.
[c]Statistical *t*-test between means.
[d]Generalized linear model (GLM) between means.

Table 3 shows mean 8-OHdG levels among never smokers by tertile levels of dCO_2 and TVOCs exposure. The mean (SD) values increased from 3.10 (1.56) μg/g creatinine at the lowest dCO_2 and TVOCs tertile levels to 6.27 (3.03) μg/g creatinine at the highest tertile levels.

Further logistic regression analysis revealed that the crude OR for the elevated 8-OHdG level was significantly higher for (1) often use chemicals to sanitize, (2) not sensitive to ETS, (3) not sensitive to chemical, and those with (4) lower temperature (below 23.8 °C), (5) lower relative humidity (below 55.8%), (6) dCO_2 levels at the second tertile level (between 390 and 680 ppm) and greater, and (7) TVOCs exposure at the second tertile level (between 114 and 360 ppb) and greater (Table 4). In the multivariate logistic regression analysis, the factors remained a significant association with 8-OhdG were sensitive to ETS, and exposure to dCO_2 and TVOCs. The 8-OHdG levels had a significant dose-response relation with dCO_2 level ($P = 0.03$). Individuals with the exposure at the highest tertile dCO_2 level had an OR of 3.37 (95% CI = 1.20–9.46). However, the association with TVOCs exposure at the highest tertile level became non-significant. Individuals sensitive to ETS were protected from having higher 8-OHdG levels in urine (OR = 0.53; 95% CI = 0.29–0.98). But, the ETS exposure was not a significant factor in the model.

4. Discussion

Occupational exposure to chemicals has been associated with the considerable increase of urinary 8-OHdG concentration, such as engine oil (Nilsson et al., 2004), benzene exposure (Lagorio et al., 1994), styrene and chromium (Kuo et al., 2003; Marczynski et al., 1997), coal-tar-pitch dust and/or asphalt fume (Toraason, 1999) and traffic exhaust (Chuang et al., 2003). Heavy industry exposure

Table 3
Means (and standard deviations) of urinary 8-hydroxydeoxyguanosine[a] by tertile levels of dCO_2[b] and TVOCs[c] exposure in offices for non-smoking employees ($N = 344$)

Exposure index	dCO_2, ppm				
	<390	390–680	>680	Total	*P*-value
TVOCs, ppb					
<114	3.10 (1.56)	4.91 (2.41)	—	3.96 (2.20)	<0.001[d]
114–360	4.60 (2.50)	5.07 (2.63)	6.65 (2.55)	5.06 (2.62)	
>360	—	6.67 (3.65)	6.27 (3.03)	6.34 (3.14)	
Total	3.80 (2.18)	5.28 (2.80)	6.32 (2.97)	5.15 (2.86)	<0.001[e]
P-value				<0.001[e]	

[a]8-hydroxydeoxyguanosine, μg/g creatinine shown in table field.
[b]Difference between indoor and outdoor carbon dioxide.
[c]Indoor total volatile organic compounds.
[d]Statistical test: analysis of variance.
[e]*P* for trend.

Table 4
Odds ratios of having urinary 8-OHdG[a] greater than overall median, 4.53 μg/g creatinine, by dCO_2[b] and TVOCs[c] obtained from univariate and multivariate logistic regression[d] for non-smoking office employees ($N = 344$)

	Crude OR[e]	95% CI	Adjusted OR	95% CI
Gender				
Female	1.00		1.00	
Male	1.26	0.73–2.17	1.09	0.59–2.01
P-value	0.41		0.51	
Age (year)				
<40	1.00		1.00	
>40	0.92	0.59–1.45	1.02	0.61–1.71
P-value	0.73		0.73	
Working hours per day				
<9	1.00		1.00	
>9	1.23	0.81–1.88	1.41	0.87–2.28
P-value	0.33			
Sanitizing by using chemicals				
Never or sometimes	1.00		1.00	
Often	1.79	1.11–2.90[f]	1.29	0.75–2.20
P-value	0.02[f]		0.12	
Environmental tobacco smoking sensitivity				
No	1.00		1.00	
Yes	0.49	0.30–0.81[f]	0.53	0.28–0.98[f]
P-value	0.01[f]		0.07	
Chemical sensitivity				
No	1.00		1.00	
Yes	0.51	0.32–0.80[f]	0.80	0.45–1.42
P-value	<0.01[f]		0.52	
Exposure to secondhand smoke				
No	1.00		1.00	
Yes	1.44	0.82–2.51	1.27	0.69–2.35
P-value	0.21		0.27	
Room temperature (°C)				
<23.8	1.00		1.00	
≧23.8	0.48	0.31–0.74[f]	0.98	0.51–1.87
P for trend	<0.01[f]		0.55	
Relative humidity (%)				
<55.8	1.00		1.00	
≧55.8	0.57	0.37–0.87[f]	0.91	0.53–1.56
P for trend	0.01[f]		0.68	
dCO_2 (ppm)				
<390	1.00		1.00	
390–680	1.94	1.13–3.32[f]	1.74	0.92–3.29
≧680	4.83	2.75–8.46[f]	3.37	1.20–9.46[f]
P for trend	<0.01[f]		0.03[f]	
TVOCs (ppb)				
<114	1.00		1.00	
114–360	2.68	1.54–4.64[f]	2.62	1.43–4.79[f]
≧360	4.59	2.65–7.96[f]	1.94	0.79–4.74
P for trend	0.05[f]		0.12	

[a]8-hydroxydeoxyguanosine.
[b]Difference between indoor and outdoor carbon dioxide.
[c]Indoor total volatile organic compounds.
[d]Multivariate analysis adjusted for sex, age, working hours per day, sanitizing by using chemicals, environmental tobacco smoking and chemical sensitivity, environmental tobacco smoke exposure, temperature, relative humidity, dCO_2, and TVOCs.
[e]Odds ratios.
[f]Statistically significance ($P<0.05$).

may confound the contribution of smoking to oxidative DNA stress (Loft and Poulson, 1998; Toraason, 1999). With no industrial chemical exposure, there has been no study investigating factors associated with 8-OHdG for non-smoking employees in high-rise building offices.

This study used urinary 8-OHdG to represent DNA damage associated with the exposure of indoor air pollution among non-smokers at offices of high-rise buildings. There were wide ranges in the concentrations of both dCO_2 and dTVOC (Table 1), reflecting a large

variation in indoor accumulation of pollutants. The range of 8-OHdG measured was also wide and had significant associations with both dCO_2 and dTVOC. Age could influence the excretion of 8-OHdG in human tissues and in urine (Mecocci et al., 1993). However, we did not find this kind of association in the present study (Table 2). Hayakawa et al. (1991) have reported the slowed accumulation of 8-OHdG in mitochondrial DNA of the elderly subjects aged over 65. Most participants in this study were younger than 50 (83.4%) and the effect of age-associated accumulation of 8-OHdG in human DNA was not observed. Kimura et al. (2006) also reported the mean concentrations of 8-OHdG in urine were not significantly different between age groups (<45 vs. $\geqslant 45$ years) and between males and females for healthy Japanese people. The oxidative damage occurs rapidly after exposure, and this damage can be repaired rapidly (Wong, et al., 2005). The oxidative DNA damage is expected to be associated with the exposure time (i.e., hours at the offices). The multivariate analysis shows that participants working for longer than 9 h had higher urinary 8-OHdG than those working for fewer hours; but the difference was not significant. This is because the indoor air pollution levels vary among offices and the contribution of exposure time may become less significant.

The measured urinary 8-OHdG values in this study may exclude most the effects from both traffic exhaust and tobacco smoke. The levels of dCO_2 and TVOCs measured in the offices represented indoor pollution the study participants exposed to. Their average (SD) urinary 8-OHdG level of 5.15 (2.86) μg/g creatinine, indicating a substantial DNA damage was due to oxidative stress from indoor pollution instead of the exposure to chemicals in traffic exhaust and tobacco smoke.

An earlier study in the same city found that the average (SD) urinary 8-OHdG values were 12.2 (3.4) μg/g creatinine in non-smoking taxi drivers associated with traffic exhaust exposure and 13.3 (4.5) μg/g creatinine in community men associated with smoking (Chuang et al., 2003). Lai, et al. (2005) reported a similar average level, 13.3 (7.1) μg/g creatinine of urinary 8-OHdG for highway toll station workers. Zagury et al. (2000) also reported a higher black smoke exposure for taxi drivers in Paris. It is not possible to affirm that at the largest levels of 8-OHdG is due to the oxidative stress induced by environmental exposure. Air pollution contains a large amount of free radicals. Although cells have developed various enzymatic and non enzymatic systems to control excited oxygen species such as the superoxide radical (O^{2-}), singlet oxygen ($^{\bullet}O$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($^{\bullet}OH$), excessive generation of them within tissues may damage proteins, lipids and nucleic acids (Yin et al., 1995).

The excretion of urinary 8-OHdG has been correlated with ETS exposure (Loft and Poulsen, 1996). In the present study, participants who were sensitive to ETS might have avoided the exposure. Therefore, we failed to find a significant association between ETS and the urinary 8-OHdG levels. Smith et al. (2001) also reported that nonsmokers exposed to ETS for at least five hour per day do not have significantly increased 8-OHdG levels.

Carbon dioxide, tobacco smoking, secondhand smoke, temperature, dampness and VOC have been noticed in sick building syndrome (SBS) etiologic studies (Bako-Biro et al., 2004; Engvall et al., 2001; Kim et al., 2002; Lyles et al., 1991; Norback and Edling, 1991; Pommer et al., 2004; Sari et al., 2004; Skov et al., 1989). CO_2 is thought to be the major factor associated with SBS symptoms (Apte et al., 2000; Backman and Haghighat, 1999; Bourbeau et al., 1997; Seppänen et al., 1999). It is understood that there is no direct causal link between exposure to CO_2 and SBS symptoms, but rather CO_2 is approximately correlated with other indoor pollutants that may cause symptoms. We also suspect CO_2 of having association with DNA damage effect as shown in the 8-OHdG relationship. It is likely that this association is from other factors correlated with CO_2, in addition to TVOCs.

The primary source of indoor CO_2 for office buildings is generated from the respiratory of employees and bio-effluents, varied with the ventilation rate in the office (ACGIH, 1991; ASHRAE, 2001). Higher indoor CO_2 concentration reflects lower per occupant ventilation rate, with less fresh air supply to the rooms. The difference between indoor and outdoor CO_2 concentrations can be used as a surrogate measure for building ventilation in an office (Apte et al., 2000). Inefficient ventilation increases indoor air pollution, such as TVOCs.

In this study, the average indoor CO_2 and TVOCs concentrations at the offices were 2.6 and 6.7 times, respectively, higher than those in the air outside the buildings. The concentrations were with a large variation among offices, with ranges from 0.8 to 6.8 times for CO_2 and from 0.5 to 131.3 times for TVOCs. With no consideration of the effect of TVOCs of higher levels, the average (SD) urinary 8-OHdG was 3.80 (2.18) μg/g creatinine for persons at the offices with the dCO_2 levels at the lowest tertile range. On the other hand, the VOCs are also common indoor air pollutants have been observed in the previous studies (Brasche et al., 2004; Pejtersen et al., 2001; Pitten et al., 2000; Takigawa et al., 2004). The TVOCs have significant associations with skin hydration for the level of higher than 666 $\mu g/m^3$ (289 ppb) (Brasche et al., 2004), and with sore throat, irritations of mucous membrane, headache, and weariness for the level of higher than 990 $\mu g/m^3$ (391 ppb) (Pitten et al., 2000). Some other studies have reported the TVOCs levels in copy centers ranging from <71 to 21,300 ppb (Stefaniak et al., 2000).

In this study, the TVOCs levels in offices with the lowest tertile ranging from 6 to 114 ppb, were somewhat lower than the average outdoor level of 181 ppb. At this tertile interval, the mean (SD) 8-OHdG was 3.96 (2.20) μg/g creatinine with no consideration of the effect of dCO_2 of higher levels. The mean (SD) urinary 8-OHdG of 3.10 (1.56) μg/g creatinine in the lowest tertiles of dCO_2 and TVOCs may represent the back ground level effect with no

effect from additional indoor air pollutants. The increase of mean urinary 8-OHdG was on a parallel with the increase of dCO_2 and indoor TVOCs as shown in Table 3. The strong dose-response relationship between average urinary 8-OHdG levels and tertile levels of dCO_2 and TVOCs demonstrated a significant interaction relationship between dCO_2 level and TVOCs exposure.

To our knowledge, this is the first study on how the urinary 8-OHdG levels are associated with the ventilation status at office. It is interesting to note in the univariate logistic regression analysis that both dCO_2 and TVOCs were significantly associated with elevated 8-OHdG levels. But, in the multivariate analysis, the association with TVOCs is less strong than with dCO_2. Individuals who are sensitive to ETS may take action to avoid exposing to the secondhand smoke and protected from the oxidative stress for 47%. The dCO_2 levels remained as independent predictors of the elevated 8-OHdG levels with a significant dose-response relationship. We hypothesize that the relationship between per person ventilation rate (as traced by dCO_2) and oxidative stress in office employees is biological credible.

In conclusion, this study found significant association between urinary 8-OHdG and the exposure to CO_2 and TVOCs in the office. The dose-response association with dCO_2 is of particularly interesting. This association reflects the effect of ventilation efficiency in each office. The VOC exposure could not explain all urinary 8-OHdG measured. Other components deserve further investigation. This association cannot be dismissed and may indicate potential to reduce oxidative stress of employees at work through large increase in ventilation rates.

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