Urinary 8-hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage in workers exposed to fine particulates.

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Residual oil fly ash (ROFA) is a particularly polluting generated by the combustion of fuel oil. The chemical composition of ROFA includes sulfates, silicates, carbon- and nitrogen-containing compounds, and metals (Ghio et al. 2002). Of particular interest is the significant presence of bioavailable transition metals in ROFA, including vanadium, iron, and nickel and, to a lesser extent, chromium, manganese, and copper (Huffman et al. 2000). Exposure to ROFA, specifically the soluble metal component, has been shown to induce acute lung injury and airway inflammation in both animals and humans (Costa and Dreher 1997; Dreher et al. 1997; Gavett et al. 1997; Ghio et al. 2002; Hauser et al. 1995a, 1995b; Williams 1952; Woodin et al. 1998, 2000).

The carcinogenicity of ROFA itself has not been studied widely; however, several of the metals present in ROFA have been found to be carcinogenic (Hayes 1997; Nemery 1990). Occupational exposures to nickel and chromium were associated with an excess risk of lung and nasal cancer (Andersen et al. 1996; Anttila et al. 1998; Gibb et al. 2000). A recent study by the U.S. National Toxicology Program indicated that chronic inhalation exposure to vanadium pentoxide also might be carcinogenic, as evidenced by the increased incidence of alveolar/bronchiolar neoplasms in mice (Ress et al. 2003).

Although the carcinogenicity of certain metals has been recognized, the mechanism leading to the development of cancer is unclear. A possible mechanism is the induction of oxidative DNA damage by reactive oxygen species (ROS) (Hartwig 2000; Knaapen et al. 2002). Transition metals serve as catalysts in the generation of ROS through a Fenton-like chemical reaction (Pritchard et al. 1996). In addition to inducing oxidative DNA damage, metals may enhance further their carcinogenicity by interfering with DNA repair processes (Hartwig 2000).

The urinary excretion of 8-hydroxy-2′-deoxyguanosine (8-OHdG) is often used as a biomarker to assess the extent of repair of ROS-induced DNA damage in both the clinical and occupational setting (Erhola et al. 1997; Honda et al. 2000; Lagorio et al. 1994; Pilger et al. 2000; Tagesson et al. 1993; Toraison et al. 2001). 8-OHdG is formed from a hydroxyl radical attack at the C-8 position of deoxyguanosine in DNA (Kasai et al. 1986). In a study of patients with small-cell carcinoma of the lung, elevated urinary 8-OHdG concentrations were observed compared with those of control subjects (Erhola et al. 1997). In workers exposed occupationally to benzene, a known carcinogen, a dose–response relationship was found between personal exposure to benzene and urinary 8-OHdG concentrations (Lagorio et al. 1994). Exposed workers in the asbestos, rubber, and azo-dye industries also were found to have significantly higher urinary 8-OHdG levels than those of nonexposed workers (Tagesson et al. 1993).

In this study, we investigated the association between personal exposure to fine particulate matter with an aerodynamic mass median diameter ≤ 2.5 µm (PM_{2.5}) and oxidative DNA damage and repair, as indicated by urinary 8-OHdG levels. PM_{2.5} vanadium, manganese, nickel, and lead exposures also were positively associated with 8-OHdG levels (p ≤ 0.05). This study suggests that a relatively young and healthy cohort of boilermakers may experience an increased risk of developing oxidative DNA injury after exposure to high levels of metal-containing particulate matter. Key words: biomarkers, epidemiology, occupational, oxidative DNA damage, particulate matter. Environ Health Perspect 112:666–671 (2004). doi:10.1289/ehp.6827 available via http://dx.doi.org/ (Online 20 January 2004)
the 27 eligible boilermakers participated in the study, for a participation rate of 74%. The subjects were monitored during a 5-day work period in June 1999 using a repeated-measures study design. Self-administered questionnaires were used to obtain information on medical history, including respiratory symptoms and diseases, smoking history, and occupational history.

The overhaul entailed removing and replacing the interior wall panels and water-circulating tubing of the boilers and repairing the ash pit. Subjects at the overhaul site were exposed to fine particulate matter from ROFA as well as that from typical boiler-making operations such as welding, burning, and grinding.

**Particulate sample collection.** The collection of particulate samples using personal exposure monitors (PEMs) has been described previously (Kim et al. 2003b). Briefly, subjects were randomly selected to wear PEMs during their workshift. The model 200 PEM (MSP Corporation, Minneapolis, MN) with a 2.5-µm impactor cut size was used in line with a Gillain GillAir-5 pump (Sensidyne Inc., Clearwater, FL) calibrated at a flow rate of 4 L/min. The air sample was collected on a polytetrafluoroethylene membrane filter (Gelman Laboratories, Ann Arbor, MI). The mass collected on the filter was divided by the air volume sampled to calculate the gravimetric PM$_{2.5}$ concentration. PM$_{2.5}$ concentrations were standardized to 8-hr time-weighted averages (TWA).

**Metal analysis of particulate samples.** Metal analysis of particulate filter samples has been described previously (Kim et al. 2003a). Briefly, filter samples were digested using a modified acid digestion procedure originally developed by Loring and Rantala (1992). The digestion protocol allowed for the determination of total metal concentration, including metal oxides. The filter was placed in a Teflon liner (Parr Instrument Co., Moline, IL), and 5 mL nitric acid (OPTIMA, Seastar Chemical Inc., Pittsburgh, PA) and 400 µL hydrofluoric acid (OPTIMA, Seastar Chemical Inc.) were added to the liner. The Teflon liner was placed in a Parr bomb (Parr Instrument Co.) and heated in a microwave oven for 3 min at 750 watts. After cooling, 10 mL of 1.5% boric acid (ULTREX, J.T. Baker, Phillipsburg, NJ) was added to theliners, and the sample was reheatred for 3 min. After an additional cooling period, the digestate was transferred into a 50-mL polypropylene tube and diluted to 50 mL with ultrapure deionized water.

Samples were analyzed using inductively coupled plasma–mass spectrometry (ICP-MS; Perkin-Elmer/SCIEX ELAN model 5000 and model 6100; Perkin-Elmer Inc., Norwalk, CT). Elements analyzed were vanadium, chromium, manganese, nickel, copper, and lead. Quality assurance and control procedures were performed to ensure the accuracy and precision of the metal analysis data.

The limit of detection (LOD) was determined as three times the standard deviation of 10 replicate measurements of the filter blank samples. None of the metal concentrations were below the LOD. The mass of each metal was calculated after adjusting for the blank filter metal concentration. The PM$_{2.5}$ metal concentrations were calculated by dividing the metal mass by the air volume sampled. The PM$_{2.5}$ metal contents were calculated by dividing the PM$_{2.5}$ metal mass by the total PM$_{2.5}$ mass.

**Urine sample collection.** The collection of urine samples began on the first day of the work week before work had begun. Urine samples were collected pre- and post-workshift each day during the 5-day sampling period. After samples were collected in sterile 120-mL urine collection cups, they were aliquoted into 15-mL polypropylene tubes. Specimens were stored at −20°C until analysis.

**Urine analysis for creatinine.** A polypropylene tube containing 5 mL frozen urine was sent to ESA Laboratories, Inc. (Chelmsford, MA) for creatinine analysis. The creatinine level in the urine sample was measured with a Shimadzu model UV-1601 spectrophotometer (Shimadzu Corporation, Nakagyou-ku, Kyoto, Japan) using the Jaffé reaction (Jaffé 1886).

**Urine analysis for cotinine.** Urinary analysis of cotinine also was performed at ESA Laboratories. Urinary cotinine was determined using reverse-phase high-performance liquid chromatography with ultraviolet spectrophotometry detection (Haritaharan and VanNoord 1991).

**Urine analysis for 8-OHdG.** Urine analysis for 8-OHdG was performed by Genox Corp. (Baltimore, MD). Urinary 8-OHdG was determined using a competitive enzyme-linked immunosorbent assay (Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan; Erhola et al. 1997; Leinonen et al. 1997). Briefly, 50 µL of urine samples and standards were added to precoated 8-OHdG protein conjugate microtiter plates, followed by 50 µL of the primary antibody, anti-8-OHdG monoclonal antibody solution, and incubated for 1 hr at 37°C. The plates were washed and the enzyme-labeled horseradish peroxidase–conjugated secondary antibody (100 µL) was applied for 1 hr at 37°C. After washing, 100 µL of the chromatic substrate, (3’,3’,5’,5´)-tetramethylbenzidine, was added to the plate and allowed to react at room temperature for 15 min. The intensity of color produced for each sample was measured at an optical density of 490 nm. Pooled urine samples from several healthy adults were used as the quality control (QC) samples. For each standard 96-well microplate, six to nine QC samples were randomly placed among the unknown samples. The measured QC values were averaged and compared with previously established values. Acceptable QC values were defined as mean ± 2 SDs. The LOD for 8-OHdG was 0.64 ng/mL. For each subject sample, either a duplicate or triplicate measurement was performed. The mean, SD, and coefficient of variation (percent) were calculated. Any sample with a coefficient of variation equal to or greater than 20% was retested. The urinary 8-OHdG concentration was adjusted to the urinary concentration of creatinine (micrograms 8-OHdG/grams creatinine) to control for the variability in urine dilution.

**Statistical analysis.** Statistical analyses were performed using SAS version 6.12 (SAS Institute Inc., Cary, NC). The medians and interquartile ranges (25th–75th percentiles; Q25–Q75) of the occupational total PM$_{2.5}$ concentration and of the vanadium, chromium, manganese, nickel, copper, and lead concentrations in PM$_{2.5}$ were determined for all subjects. Medians are presented for the PM$_{2.5}$ exposures because of the positively skewed distribution of the data. Wilcoxon rank-sum tests were performed to compare the occupational PM$_{2.5}$ concentrations in smokers and nonsmokers. The Spearman rank correlation coefficient was used to determine the correlation between total PM$_{2.5}$ and the individual PM$_{2.5}$ metal concentrations, and the correlations among the individual PM$_{2.5}$ metal concentrations.

Urinary creatinine-adjusted 8-OHdG concentrations (micrograms/grams creatinine) were used in all analyses. Because of the repeated measurements design, linear mixed models were used to calculate the mean pre-workshift and post-workshift measurements. Pre-workshift measurements served as baseline measurements. A cross-shift change in 8-OHdG level was calculated by subtracting the pre-workshift concentration from the post-workshift concentration. Linear mixed models were used to compare the pre-workshift 8-OHdG levels in smokers and nonsmokers and to compare pre-workshift and post-workshift 8-OHdG concentrations.

Linear mixed regression models were constructed to investigate the association between urinary 8-OHdG concentrations and total PM$_{2.5}$ and PM$_{1.5}$ metal concentrations. To adjust for total PM$_{2.5}$ exposure, analyses also were performed using PM$_{2.5}$ metal content as the exposure of interest. Although urinary 8-OHdG data collection was complete, some PM$_{2.5}$ exposure data were missing at random because subjects were randomly selected each day to wear exposure monitors. Therefore, all analyses were restricted to subjects who had both urinary 8-OHdG and the corresponding PM$_{2.5}$ concentrations on a given day. A generalized autoregressive covariance structure was used because it resulted in the best Akaike's Information Criterion (AIC) for the models.
Information Criterion compared with models with other covariance structures (Verbeke and Molenberghs 1997). A generalized autoregressive structure assumes that the correlation function decays exponentially as the interval between the measurements increases (Verbeke and Molenberghs 1997). Restricted maximum likelihood was used to estimate the covariance parameters. Regression models were adjusted for tobacco smoking, chronic bronchitis status (yes/no), and age because previous studies have found these variables to be significantly associated with urinary 8-OHdG levels (Igishi et al. 2003; Loft et al. 1992; Pilger et al. 2001). According to the American Thoracic Society (ATS) criteria, chronic bronchitis is defined as the presence of a productive cough most days of the week for 3 months or more in at least 2 consecutive years (ATS 1995). The effect of smoking was evaluated using self-reported current smoking status (yes/no) and creatinine-adjusted urinary cotinine concentrations (micrograms/grams creatinine). In addition, to study effect modification by smoking, an interaction term between PM$_{2.5}$ exposure and a smoking variable was included in the model. The level of significance for all analyses was set at 0.05.

Results

Study population demographics. The study population demographic data are presented in Table 1. The study population consisted of 20 men, all of whom were white. Their ages ranged from 18 to 59 years, with a mean ± SD of 45.5 ± 12.0 years. On average, the subjects had 21.7 ± 12.9 years of boilermaking experience. Four of the 20 subjects (20%) had chronic bronchitis as defined by ATS (ATS 1995). Ten of the 20 subjects (50%) were current cigarette or cigar smokers. The median urinary creatinine-adjusted cotinine levels were 414 µg/g creatinine (range, 5–2,373) for smokers and 12 µg/g creatinine (range, 3–72) for nonsmokers. None of the demographic characteristics significantly differed between the 20 subjects who participated and the 7 nonparticipants (p > 0.25).

Particulate exposure assessment. The personal occupational PM$_{2.5}$ exposure data are shown in Table 2. Workplace particulate samples were collected from 19 of the 20 subjects.

The number of workdays each subject wore the PEM varied from 4 days to none. The subjects, on average, worked 10-hr shifts at the power plant. Particulate samples were collected for 8.9 ± 1.3 hr. The median total PM$_{2.5}$ 8-hr TWA concentration was 0.44 mg/m$^3$, with an interquartile range of 0.29–0.76 mg/m$^3$, for all subjects. The total PM$_{2.5}$ 8-hr TWA concentrations were not significantly different between smokers and nonsmokers (p = 0.74).

Of the six metals, the subjects had the highest exposure to vanadium (median, 1.23 µg/m$^3$; Q$_{25}$–Q$_{75}$, 0.47–3.53) and the lowest exposure to chromium (median, 0.11 µg/m$^3$; Q$_{25}$–Q$_{75}$, 0.05–0.27). Each of the constituent metal concentrations were moderately to highly correlated with the total PM$_{2.5}$ concentrations, ranging from a Spearman correlation coefficient of 0.48 (p = 0.002) for PM$_{2.5}$ manganese to 0.78 (p = 0.001) for PM$_{2.5}$ nickel. The individual metal concentrations also were moderately to highly correlated with one another (0.52 < r < 0.92; p < 0.001).

Urinary 8-OHdG analysis. Day 1 pre-workshift urine samples were collected after an average of 2 days away from work. The mean urinary creatinine-adjusted 8-OHdG concentrations (± SE) for each pre- and post-workshift sampling time are shown in Figure 1. The mean ± SE pre-workshift 8-OHdG concentration was 13.26 ± 1.04 µg/g creatinine for all subjects (Table 3). Current smokers had a mean baseline 8-OHdG concentration of 12.09 ± 0.65 µg/g creatinine, whereas nonsmokers had a mean baseline 8-OHdG concentration of 14.84 ± 2.07 µg/g creatinine. The mean pre-workshift 8-OHdG concentrations were not significantly different between smokers and nonsmokers (p = 0.20).

The pre-workshift 8-OHdG concentrations were compared with the post-workshift samples. The mean ± SE of the cross-shift change was 1.88 ± 0.74 µg/g creatinine for all subjects. The cross-shift samples were found to be not significantly different compared with the post-workshift samples (p = 0.02). The cross-shift changes in urinary 8-OHdG concentrations were not significantly different in smokers compared with nonsmokers (p = 0.83).

Association between urinary 8-OHdG concentrations and PM$_{2.5}$ exposure. Linear mixed regression models were constructed to investigate the association between urinary 8-OHdG concentrations and PM$_{2.5}$ exposure. Crude analyses indicated a significant association between PM$_{2.5}$ 8-TWA concentrations and urinary 8-OHdG concentrations (p = 0.02). Each 1 µg/m$^3$ of PM$_{2.5}$ exposure was associated with a 1.68 µg/g creatinine [95% confidence interval (CI), 0.24–3.12] increase in urinary 8-OHdG concentration.

The effects of tobacco smoking, chronic bronchitis status, and age were investigated. Both self-reported smoking status (yes/no; p = 0.85) and urinary cotinine levels (p = 0.28) were not found to be significant predictors of urinary 8-OHdG in the models adjusted for chronic bronchitis status and age. In addition, smoking was not found to be a confounder of the association between urinary 8-OHdG and PM$_{2.5}$ exposure. However, both age and having chronic bronchitis were found to be statistically significant predictors of urinary 8-OHdG in the adjusted model. Each year of age was associated with a 0.18 µg/g creatinine (95% CI, 0.02–0.35) increase in urinary 8-OHdG concentrations, after adjusting for PM$_{2.5}$ exposure, urinary cotinine levels, and chronic bronchitis status. In addition, the urine 8-OHdG concentrations in subjects with chronic bronchitis were, on average, 8.37 µg/g creatinine (95% CI, 3.41–13.33) greater than subjects without chronic bronchitis in the adjusted model.

The association between urinary 8-OHdG levels and PM$_{2.5}$ exposure remained statistically significant, after adjusting for urinary cotinine levels, chronic bronchitis status, and age (Table 4). Each 1 mg/m$^3$ increase in total PM$_{2.5}$ 8-hr TWA concentration was associated with an increase in urinary 8-OHdG concentrations by 1.67 µg/g creatinine (95% CI, 0.21–3.14), after adjusting for urinary cotinine levels, chronic bronchitis status, and age. PM$_{2.5}$ vanadium, manganese, nickel, and lead concentrations also showed a statistically significant association with 8-OHdG concentrations (p ≤ 0.05). Each 1 µg/m$^3$ increase in PM$_{2.5}$ vanadium exposure was associated with an increase of 0.23 µg/g creatinine (95% CI, 0.10–0.36).

![Figure 1](image-url)  
**Figure 1.** The mean urinary creatinine-adjusted 8-OHdG concentrations (± SE) for each pre-workshift and post-workshift sampling time. The mean post-workshift urinary 8-OHdG concentration is significantly different from the mean pre-workshift concentration (p = 0.02).
0.04–0.42) in 8-OHdG concentrations, after adjusting for urinary cotinine levels, chronic bronchitis status, and age. Likewise, with each 1-µg/m³ increase of PM₂.₅ manganese, nickel, and lead exposure, 8-OHdG concentrations increased by 0.47 µg/g creatinine (95% CI, 0.05–0.89), 0.33 µg/g creatinine (95% CI, 0.01–0.64), and 1.64 µg/g creatinine (95% CI, 0.02–3.26), respectively. PM₂.₅ chromium exposure was marginally associated with urinary 8-OHdG concentrations (p = 0.09).

Because of the high correlation between the total PM₂.₅ concentration and the individual PM₂.₅ metal concentrations, total PM₂.₅ exposure could not be directly adjusted for in the models investigating the association between PM₂.₅ metal concentrations and urinary 8-OHdG levels. To adjust for total PM₂.₅ exposure, analyses were performed using PM₂.₅ metal contents, calculated by dividing the mass of the individual metal by the total PM₂.₅ mass. The regression coefficients for the PM₂.₅ metal contents are summarized in Table 4. Analyses using PM₂.₅ metal contents, in general, indicated results similar to analyses from PM₂.₅ metal concentrations. The PM₂.₅ metal contents of vanadium, manganese, and nickel were significantly associated with urinary 8-OHdG concentrations, after adjusting for urinary cotinine levels, chronic bronchitis status, and age (p ≤ 0.03). Each 1,000-µg/g increase in PM₂.₅ vanadium, manganese, and nickel content was associated with a 0.19-µg/g creatinine (95% CI, 0.05–0.33), 0.22-µg/g creatinine (95% CI, 0.05–0.39), and 0.21-µg/g creatinine (95% CI, 0.02–0.41) increase in 8-OHdG concentration, respectively. Chromium, which had been marginally significant in the analysis using metal concentration, almost reached statistical significance (p = 0.05) when its metal content was used in the analysis. In contrast, lead, which had previously been statistically significant became marginally significant (p = 0.10) when analysis was performed using its metal content. In both analyses using metal content and metal concentration, copper was not found to be significantly associated with urinary 8-OHdG concentrations.

Analyses using self-reported smoking status (yes/no) suggested that the association between 8-OHdG levels and total PM₂.₅ exposure might be modified by tobacco smoking (p = 0.12). However, regression analysis using urinary cotinine concentrations found that smoking did not significantly modify the association between urinary 8-OHdG levels and total PM₂.₅ concentrations (p = 0.66).

Discussion

The proportion of lung cancer attributable to occupational exposure to recognized carcinogens ranges from 8.8 to 40%, after controlling for confounding by smoking (Simanato et al. 1988). Among the occupational exposures, lung cancer is most frequently associated with asbestos, radon, and metal exposures (Nemery 1990). The carcinogenicity of metals may derive from their ability to induce oxidative DNA damage through the generation of ROS (Hartwig 2000; Knaapen et al. 2002; Pritchard et al. 1996). In this study, we investigated a urinary biomarker for oxidative DNA damage and repair, 8-OHdG, in boilermakers exposed to ROFA and metal fumes.

The particulate exposure in our cohort of boilermakers was higher than levels typically experienced by the general population. The median occupational PM₂.₅ exposure in our study was 440 µg/m³, compared with PM₂.₅ concentrations ranging from 10 to 30 µg/m³ in typical U.S. urban air (Dockery et al. 1993). Despite the high exposure in this study, the PM₂.₅ levels were much lower than the Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) of 5 mg/m³ for respirable fraction particulates (OSHA 1997). In addition, none of the particulate samples had vanadium, manganese, nickel, or copper, or lead concentrations exceeding the OSHA PELs (OSHA 1997). Among all the PM₂.₅ metal concentrations, only one sample for nickel exceeded the more stringent National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits (NIOSH 2003).

Previous studies provide evidence that occupational exposure to certain metals may be associated with increased risk of cancer. Mancuso (1997) found an exposure–response relationship between chromium exposure and age-specific lung cancer death rates in workers previously employed at a chromate plant. In a study at a nickel refinery, workers with the highest cumulative soluble nickel exposures had a 3-fold increase in relative risk of lung cancer compared with the control population (Andersen et al. 1996). Other epidemiologic studies also found an excess of lung cancer deaths in battery plant workers chronically exposed to lead (Cooper et al. 1985; Wong and Harris 2000). However, most studies did not effectively control for other confounding factors such as smoking and coexposure to other potential carcinogens. In our study, potential confounding by smoking was adjusted for using urinary cotinine concentrations. Urinary cotinine is a reliable biomarker that provides an accurate measure of smoking dose in smokers and environmental tobacco smoke exposure in nonsmokers (Husgafvel-Pursiainen 2002).

In this study, we found a significant exposure–response relationship between total PM₂.₅ and urinary 8-OHdG levels in workers exposed to ROFA and welding fumes. With each 1-mg/m³ increase in total PM₂.₅ exposure, urinary 8-OHdG concentrations increased by 1.67 µg/g creatinine, a 13% increase from baseline levels. Similarly, statistically significant associations were seen between urinary concentrations of 8-OHdG and PM₂.₅ vanadium, manganese, nickel, and lead concentrations (p ≤ 0.05). PM₂.₅ chromium exposure was marginally associated with increased urinary 8-OHdG (p = 0.09). Similar results were observed using PM₂.₅ metal contents as the exposure of interest, suggesting that the metal...
components of PM2.5 that may contribute to and metal fumes. However, there may be other nary levels of 8-OHdG after metal-containing urinary 8-OHdG concentrations. Increased urinary 8-OHdG levels were elevated in both smokers and nonsmokers after occupational PM2.5 exposure (p = 0.02). The PM2.5 concentrations were not significantly different between smok- ers and nonsmokers (p = 0.74), indicating that the contribution of smoking to total PM2.5 exposure was not significant in this population. There also was a significant association between PM2.5 vanadium exposure and oxidative DNA damage in this study. Because vanadium has a considerable presence in ROFA but not in tobacco smoke, these results indicate that occupational ROFA exposure is responsible for the oxidative DNA damage. Previous occupational studies in which workers were exposed to various carcinogens, including PAHs and asbestos, found that smoking status was not a significant predictor of urinary 8-OHdG levels (Tageesson et al. 1993; Torason 1999; Torason et al. 2001).

In conclusion, this study shows that levels of urinary 8-OHdG, a biomarker of oxidative DNA damage and repair, increased after occupational exposure to fine particulate matter. We found a positive exposure–response relation-ship between urinary 8-OHdG concentra-tions and PM2.5 exposure, specifically the PM2.5 metal component. Results from this study suggest that a relatively young and healthy cohort of boilermakers exposed to high levels of metal-containing particulate matter may experience an increased risk of developing oxidative DNA injury.

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