8-Hydroxy-2′-deoxyguanosine as a marker of oxidative DNA damage related to occupational and environmental exposures

Introduction

Reactive oxygen species (ROS) are ubiquitous in living aerobic organisms. They result either from the cells' metabolism or from the action of exogenous physical sources (e.g., ionizing radiation, UVA) and/or chemical compounds. Oxygen free radicals can induce a variety of damage to DNA, including DNA single and double strand breaks, base modifications and abasic sites (Cadet et al. 1997; Epe 1995; Dizdaroglu 1991), and they are thought to be involved in the mechanisms of ageing and in carcinogenesis (Finkel and Holbrook 2000; Beckman and Ames 1997; Wiseman et al. 1995; Feig et al. 1994). Various agents are effective in the hydroxylation of the deoxyguanosine residue in DNA. This seems to proceed via generation of an oxygen radical, such as the hydroxyl radical (Kasai and Nishimura 1986), resulting in the formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) or 2,6-diamino-4-hydroxy-5-formamidopyrimidine (Evans et al. 2004). 8-OHdG is by far the most studied oxidative DNA lesion and has gained much attention because of its mutagenic potential (Grollman and Moriya 1993). The oxidized guanine residue 8-oxoguanine can pair both in Watson-Crick mode with cytosine and in Hoogsteen mode with adenine. The latter yields G:C→T:A transversions in bacteria and human cells (Moriya and Grollman 1993; Le Page et al. 1999). As shown in cells of patients with Cockayne syndrome, deficiency in nucleotide excision repair leads to a low level of 8-OHdG repair and a high frequency of G:C→T:A transversions at the site of the lesion (Le Page et al. 1997, 1999). In addition, these transversions are frequent in human cancers and are especially prevalent in the mutational spectrum of the tumor suppressor gene p53 (Hollstein et al. 1996). This points to the significance of 8-OHdG as an endogenous mutagen and to its likely role in the process of carcinogenesis.

The cellular defense system against 8-OHdG mutagenesis involves base excision repair, nucleotide excision repair, mismatch repair and prevention of incorporation (Cooke et al. 2000). Base excision repair via DNA glycosylase (hOGG1) represents the main mechanism of protecting the integrity of the human DNA with respect to 8-OHdG. The activity of hOGG1 is responsible for the excision of 8-oxoguanine and the structurally related lesion 2,6-diamino,4-hydroxy-5-formamidopyrimidine, a hydrolytic ring-opening product of guanine. Some findings indicate that the inactivation of hOGG1 plays a role in the multistage process of carcinogenesis. The human OGG1 gene is located on the short arm of chromosome 3 (3p26), a region frequently lost in various types of cancer, especially in small-cell lung cancers where loss of heterozygosity in nearly 100% of the cases can be observed (Naylor et al. 1987; Hibi et al. 1992). Loss of one hOGG1 allele may lead to a moderate generation of 8-OHdG in DNA. However,

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loss of both alleles would abrogate hOGG1 activity imposing an increased risk of mutagenicy on the cell due to the imbalance of oxidative burden and accumulation of 8-OHdG in DNA. In healthy human cells an average oxidation rate of about 300–1,000 guanine bases per cell and day has been assessed (Loft and Poulsen 1996). Significantly higher levels of 8-OHdG have been found in tumor tissues of lung cancer patients as compared to apparently normal tissue (Olinski et al. 1992; Jaruga et al. 1994).

The formation of 8-OHdG in DNA and its urinary excretion have been frequently measured to assess oxidative stress in humans. This paper will review the use of 8-OHdG as a marker of oxidative DNA damage in occupational and environmental exposure studies, and discuss different experimental approaches.

Methods for the measurement of 8-OHdG

The most commonly measured markers of oxidative DNA damage used in human biomonitoring studies are 8-OHdG in leukocytic DNA and the excretion of 8-OHdG into urine.

Determination of 8-OHdG in DNA

High performance liquid chromatography (HPLC) with electrochemical (EC) detection

A method for the detection of 8-OHdG by HPLC-EC was introduced by Floyd et al. (1986). This technique shows subpicomolar sensitivity and has been widely applied in the last decade with various modifications. In general, the protocol involves enzymic hydrolysis to break down the DNA, separation on C18 columns and EC detection (amperometric or coulometric) of 8-OHdG. Usually the result is expressed in terms of detected 8-OHdG per amount of undamaged dG (8-OHdG/10^5 dG). Incomplete enzymatic release of 8-OHdG from DNA has been considered to cause an underestimation of the actual amount of 8-OHdG. However, there is evidence that 8-OHdG does not block the activity of nuclease P1 (Douki et al. 1997). The isolation and enzymatic digestion of DNA have been also discussed as possible sources of an artifactual oxidation of the DNA. The introduction of a chaotropic NaI method of DNA isolation and the use of desferal during homogenization resulted in a significant reduction of the 8-OHdG baseline levels in control cells (Helbock et al. 1998). In addition, the use of small quantities of DNA (< 20 µg) may be critical for the formation of artifacts. To minimize this effect, the hydrolysis of > 100 µg of DNA per sample is considered to be adequate (Helbock et al. 1998). Using a cold (0 °C) high salt guanidine thiocyanate DNA extraction technique with catalase and 2,2,6,6-tetramethylpiperidine-*N*-oxyl as antioxidants during the workup procedure, Hofer and Möller (2002) demonstrated a background level of 0.074 ± 0.027 8-OHdG/10^5 dG in human lymphocytes, which is probably the lowest value obtained yet by HPLC-EC.

Gas chromatography with mass spectrometry

Gas chromatography with mass spectrometry (GC-MS) is a highly specific, sensitive and versatile technique for the quantitative analysis of individual products of oxidized DNA bases including 8-oxoguanine (Dizdaroglu 1993). However, one drawback of this method is the possible oxidation of guanine during derivatization of 8-oxoguanine by trimethylsilylation prior to GC-MS (Hamberg and Zhang 1995; Ravanat et al. 1995). In general, the values of 8-oxoguanine obtained by GC-MS are 10- to 50-fold higher than those measured by HPLC-EC (Halliwell and Dizdaroglu 1992). The artifactual oxidation is not restricted to guanine alone, but applies also to thymine, cytosine and adenine (Douki et al. 1996), which questions the reliability of most published data based on the use of GC-MS. Prepurification of 8-oxoguanine by HPLC prior to the silylation reaction or derivatization at room temperature have been recommended to reduce artifactual formation of 8-oxoguanine (Ravanat et al. 1995; Hamberg and Zhang 1995).

^{32}P-postlabeling

^{32}P-postlabeling has been used to show that ROS are able to induce bulky adducts in vitro by direct DNA oxidation (Randerath et al. 1991). Major efforts have been made since then to develop ^{32}P-postlabeling assays for the sensitive detection of 8-OHdG. These methods are based on the enzymatic radioactive post-labeling of nucleoside 3′-monophosphates (Cadet et al. 1992; Povey et al. 1993). With ^{32}P-postlabeling, however, the samples are exposed to ionizing radiation which may cause oxidation of deoxyguanosine (dG) to 8-OHdG (Schuler et al. 1997). To reduce the risk of artifactual production of 8-OHdG during workup, it is essential to separate 8-OHdG from dG prior to postlabeling (Podmore et al. 1997; Möller et al. 1998; Zeisig et al. 1999). Recently, an improved ^{32}P-postlabeling assay for the determination of 8-OHdG in tissue DNA has been developed using a new micropreparative TLC procedure for the enrichment of 8-OHdGp prior to ^{32}P-labeling (Gupta and Arif 2001). This method shows a high sensitivity (< 1 8OHdG/10^7 dG) and needs only small amounts of DNA (1–10 μg).

Methods based on the use of formamidopyrimidine DNA N-glycosylase

Formamidopyrimidine DNA N-glycosylase (FPG) removes 8-OHGua, leaving AP sites that are converted into DNA strand breaks by the associated AP endonuclease activity. Therefore, the use of this lesion-specific enzyme allows for the introduction of extra strand breaks at sites of oxidative DNA damage. This approach has been incorporated into different methods: the single cell gel-electrophoresis (comet assay) (Dusinska and Collins 1996), the alkaline elution technique (Epe and Hegler 1994), and alkaline unwinding (Hartwig et al. 1996). These assays do not need DNA extraction and seem to be less prone to artifacts. The background levels are around 0.5 oxoguanines per 10^6 guanines in normal human cells, which is about one order of magnitude lower than

the base levels obtained by HPLC-EC (Gedik et al. 1998). A potential problem with the use of FPG is that it may not detect all the substrate.

Enzyme-linked immunosorband assay

One of the advantages of immunochemical assays is that they are relatively easy to perform. Various monoclonal and polyclonal antibodies for the determination of 8-OHdG have been developed and characterized (Yin et al. 1995; Ide et al. 1997). After extraction and digestion of DNA followed by immunoaffinity purification and enzyme-linked immunosorband assay (ELISA) quantitation of 8-OHdG, a good correlation with the values obtained by HPLC could be demonstrated. However, the levels determined by ELISA were 1.1- to 6-fold higher than those measured by HPLC-EC (Yin et al. 1995). This was explained by a possible nonspecific binding of material by the immuno-columns resulting in nonspecific inhibition in the ELISA, or crossreactivity with other modified bases present in the immunoaffinity purified samples. Evans et al. (1999) also reported a good correlation between 8-OHdG values obtained by ELISA and HPLC-EC. Their results of 8-OHdG with ELISA were about 1.8-fold higher than those measured by HPLC-EC.

Determination of 8-OHdG in urine

The rationale for the measurement of 8-OHdG in urine is based on the existence of specific repair systems for the removal of oxidative DNA damage (Cooke et al. 2000). Plasmids containing 8-OHdG were replicated only at a rate of 25 % in excision repair deficient human cells as compared to the rate of proficient cells and showed a 3- to 5-fold increased frequency of G:C→T:A transversions (Klein et al. 1992). This suggests that nucleotide excision repair is essential for the elimination of 8-OHdG in humans. The amount of modified nucleosides excreted into urine is considered to represent the whole body oxidative DNA damage, but there is no direct indication of a balance between oxidative damage of nuclear DNA and urinary excretion of 8-OHdG. To test the utility of urinary 8-OHdG, intravenous injection of 8-OHdG was applied to rats (Shigenaga et al. 1989). This showed a 66 % recovery in the first 24 h urine collection and no detectable degradation of 8-OHdG after administration and excretion. The dietary contribution to the excretion of 8-OHdG was found to be of low significance (< 2 % of the total 8-OHdG detected). Compared with the determination of 8-OHdG in leukocyte DNA, the measurement of urinary 8-OHdG offers some advantages: (1) the method is non-invasive (2) there is no production of artifacts during sample procedure or derivatization, (3) 8-OHdG undergoes no further metabolization and shows high stability in urine (Poulsen et al. 1998), and (4) the excretion of 8-OHdG is likely to reflect the oxidative DNA damage and repair from all cells in the organism. For example, an amount of 14 nmol 8-OHdG in 24 h urine would point to 140 oxidatively damaged and repaired guanines per each cell of the human body ($\sim 6 \times 10^{13}$ cells) per day. It has been argued that cell death might be a source of urinary DNA lesions, but recently Cooke et al. (2005) came to the conclusion that urinary 8-OHdG levels are independent of cell death. However, at present it is not clear to what extent the nucleotide pool contributes to

the presence of 8-OHdG in urine. Misincorporation of the damaged triphosphate 8-OH-dGTP from the nucleotide pool into DNA can be prevented by the enzyme 8-hydroxy-2′-deoxyguanosine triphosphatase which hydrolyses 8-OH-dGTP to the monophosphate 8-OH-dGMP (Bialkowski and Kasprzak 1998). Subsequent digestion of 8-OH-dGMP may give rise to 8-OHdG, which can be removed from the cell and excreted in the urine (Cooke et al. 2000).

HPLC-EC and GC-MS have been preferentially used for the analysis of 8-OHdG in urine. Separation of the analyte from the complex constituents of the urinary matrix represents a major challenge in the development of accurate methods. Therefore, many variant purification procedures have been described for HPLC techniques: e.g., solid phase extraction (Shigenaga et al. 1989), coupled-column HPLC (Loft et al. 1992; Tagesson et al. 1992; Kasai 2003), use of carbon columns (Bogdanov et al. 1999) or immunoaffinity isolation of 8-OHdG (Degan et al. 1991). In addition, solid phase extraction and/or HPLC have been used for clean-up procedure prior to GC-MS analysis of urinary 8-OHdG (Teixeira et al. 1995; Holmberg et al. 1999). HPLC systems have been also used in combination with tandem mass spectrometry (Weimann et al. 2001; Ravanat et al. 1998) and with a triple mass spectrometer (Renner et al. 2000). Recently, isotope dilution liquid chromatography with tandem mass spectrometry has been shown to be a highly specific and sensitive method for the detection of urinary 8-OHdG (Hu et al. 2004).

Erhola et al. (1997) used a monoclonal antibody based competitive ELISA for the detection of urinary 8-OHdG, accentuating some advantage of the method with respect to analyzing time and running cost. However, the values of urinary 8-OHdG were about 3- to 5-fold higher than normal 8-OHdG levels observed with HPLC-EC. Recently, fast methods for the determination of urinary 8-OHdG by capillary electrophoresis with UV detection (Kvasnicova et al. 2003) or amperometric detection (Mei et al. 2003) have been developed with detection limits of 17 μM and 20 nM, respectively.

Loft et al. (1992) identified three factors, smoking, body mass index and gender as significant determinants of urinary excretion of 8-OHdG. In smokers (n = 30, 320 ± 99 pmol 8-OHdG/kg/24 h) a 1.5-fold higher level of urinary 8-OHdG was found as compared to nonsmokers (n = 53, 213 ± 84 pmol 8-OHdG/kg/24 h). In 52 women 8-OHdG in urine was 240 ± 106 as opposed to 271 ± 96 pmol/kg/24 h in 31 men. In non-smokers, gender was the most important determinant of 8-OHdG excretion, whereas body mass index was the only significant predictor in smokers. In women, both smoking and body mass index were significantly associated with urinary 8-OHdG, whereas in men only smoking was a marginally significant predictor.

Usually published values of urinary 8-OHdG are given in pmol/kg/24 h, nmol/kg/24 h or nmol/mmol creatinine (Rev. Loft and Poulsen 1998). Frequently, spot urine samples corrected for creatinine have been used for the analysis of 8-OHdG. However, the correlation between the 8-OHdG to creatinine ratio in spot samples and the 24 h excretion of 8-OHdG has been shown to be rather poor (r = 0.5) (Poulsen et al. 1998). 8-OHdG to creatinine ratios may be adequate for crossover studies with repeated sampling in the same subjects whereas 24 h urine collecting is preferable in cross sectional studies. There is no published evidence for an artifactual formation of 8-OHdG in the organism and for its degradation upon release. In addition, 8-OHdG in urine shows high stability when stored at –20°C, as determined by repeated measurements within an interval of 6 months (Pilger et al. 2002a).

Use of 8-OHdG in occupational and environmental exposure studies

Smoking

Most of the studies on the formation of 8-OHdG in humans consider smoking as a main confounding factor, and there is substantial evidence that smokers have higher levels of 8-OHdG than non-smokers. Kiyosawa et al. (1990) observed a 1.5-fold increase in leukocyte 8-OHdG in ten healthy men after smoking two cigarettes within 10 min. This indicates that smoking may induce oxidative DNA damage in peripheral blood cells in a relatively short time. By multiple regression analysis, Loft et al. (1992) identified smoking as the most determining factor of the urinary excretion of 8-OHdG, suggesting that smoking is associated with a 50 % increase in oxidative DNA damage. However, the higher urinary excretion rate of 8-OHdG in smokers was not found to be decreased by antioxidant supplementation (D-α-tocopheryl acetate, ascorbic acid, coenzyme Q_{10}) (Prieme et al. 1997). In contrast, 4 weeks of smoking cessation resulted in a 21 % decrease in urinary 8-OHdG of 58 individuals (Prieme et al. 1998). The control group of smokers showed a 16 % higher level of 8-OHdG in urine than the smoking cessation group, and there was a significant correlation between the daily cigarette consumption and the excretion of 8-OHdG in the 123 examined smokers. Asami et al. (1996) reported a 1.88-fold higher level of 8-oxoguanine in leukocyte DNA and a 1.6-fold higher 8-oxoguanine repair capacity in smokers as compared to non-smokers. In addition, a positive correlation between the levels of 8-oxoguanine and the Brinkman index (cigarettes per day × years) was found in smokers and ex-smokers, indicating that oxidative DNA damage may be associated with the number of cigarettes smoked per lifetime. Smokers also showed a 1.43-fold higher level of 8-OHdG in non-cancerous lung tissues than non-smokers, the difference being statistically significant (Asami et al. 1997). The latter study also showed a positive correlation for the Brinkman index and 8-OHdG in the normal lung tissues from smokers and ex-smokers. Exposure to environmental tobacco smoke (ETS) has been suggested to cause oxidative DNA damage too. In 38 non-smokers exposed to ETS (as determined by plasma cotinine measurements) a 1.6-fold higher level of 8-OHdG in leukocyte DNA could be observed as compared to the control group (Howard et al. 1998). These exposed individuals showed also significantly increased levels of catalase and glutathione peroxidase in blood. Pourcelot et al. (1999) showed a 16 % higher level 8-OHdG in spot urine of 30 male smokers as compared to 30 male non-smokers, which is in good accordance with the assessed difference of 20 % in the excretion of 8-OHdG between smokers and non-smokers, derived from a longitudinal study (Pilger et al. 2001). The latter study could not confirm an effect of passive smoking on urinary 8-OHdG. Lodovici et al. (2000) observed a 2.2-fold higher level of 8-OHdG in leukocyte DNA of smokers as compared to non-smokers, whereas no correlation between the 8-OHdG levels and the number of cigarettes smoked per day could be demonstrated (Table 1).

However, not all studies confirm an effect of smoking on the production of 8-OHdG. Van Zeeland et al. (1999) even found lower levels of leukocyte 8-OHdG in smokers than in non-smokers and an inverse relationship between 8-OHdG and lifetime smoking. In

Table 1. Occupational and environmental exposure studies on 8-OHdG

Exposure	Age (year)	Sample	Assay	Mean ± SD or median	Reference
Smoking	20–22	Leukocytes	HPLC-EC	0.33 ± 0.08/10^5 dG (before smoking, n = 10) 0.51 ± 0.25/10^5 dG (after smoking, n = 10)	Kiyosawa et al. (1990)
	51 ± 7	Urine	HPLC-EC	320 ± 99 pmol/kg/24 h (smokers, n = 30) 213 ± 84 pmol/kg/24 h (non-smokers, n = 53)	Loft et al. (1992)
	44 ± 4.2 44.5 ± 4.6 45.5 ± 8.2	Leukocytes	HPLC-EC	0.59 ± 0.27/10^5 dG (smokers, n = 10) 0.40 ± 0.13/10^5 dG (ex-smokers, n = 10) 0.31 ± 0.16/10^5 dG (non-smokers, n = 10)	Asami et al. (1996)
		Urine	HPLC-EC	13.7 ± 6.1 nmol/l (male smokers, n = 12) 11.1 ± 5.6 nmol/l (male non-smokers, n = 37) 11.0 ± 4.9 nmol/l (female smokers, n = 31) 9.56 ± 4.4 nmol/l (female non-smokers, n = 63)	Tagesson et al. (1996)
	67.4 ± 11.7 75.6 ± 6.1 61 ± 16	Lung tissue	HPLC-EC	0.74 ± 0.21/10^5 dG (smokers, n = 14) 0.60 ± 0.21/10^5 dG (ex-smokers, n = 7) 0.52 ± 0.25/10^5 dG (non-smokers, n = 9)	Asami et al. (1997)
	45.6 ± 7.0	Urine	HPLC-EC	42.43 ± 19.90 nmol/24 h (smokers, n = 116)	Prieme et al. (1997)
	44.0 ± 1.4 40.1 ± 1.6	Leukocytes	HPLC-EC	28.0 ± 3.6 pg/μg (ETS exposed, n = 29) 17.2 ± 2.3 pg/μg (controls, n = 27)	Howard et al. (1998)
	44.8 ± 7.7	Urine	HPLC-EC	30.5 ± 13.9 nmol/24 h (before smoking cessation, n = 58) 24.1 ± 10.5 nmol/24 h (after smoking cessation, n = 58)	Prieme et al. (1998)
	37.9 ± 8.7 38.6 ± 9.6	Urine	HPLC-EC	20.1 ± 7.3 nmol/24 h (smokers, n = 30) 0.27 ± 0.10 nmol/kg (smokers, n = 30) 1.35 ± 0.50 nmol/mmol creatinine (smokers, n = 30) 18.4 ± 5.7 nmol/24 h (non-smokers, n = 30) 0.25 ± 0.08 nmol/kg (non-smokers, n = 30) 1.16 ± 0.35 nmol/mmol creatinine (non-smokers, n = 30)	Pourcelot et al. (1999)
	25–44	Leukocytes	HPLC-EC	2.93 ± 0.88/10^5 dG (smokers, n = 57) 3.52 ± 0.92/10^5 dG (ex-smokers, n = 16) 3.40 ± 0.65/10^5 dG (non-smokers, n = 29)	Van Zeeland et al. (1999)
	18–64	Leukocytes	HPLC-EC	2.19 ± 1.07/10^5 dG (± SE, smokers < 10 cig./d, n = 7) 4.18 ± 1.71/10^5 dG (± SE, smokers > 10 cig./d, n = 9) 1.78 ± 0.15/10^5 dG (± SE, former smokers, n = 9) 1.53 ± 0.18/10^5 dG (± SE, non-smokers, n = 31)	Lodovici et al. (2000)

Table 1. (Continued)

Exposure	Age (year)	Sample	Assay	Mean ± SD or median	Reference
	35 ± 11	Urine	HPLC-EC	24.9 ± 8.2 nmol/24 h (smokers, *n* = 23) 321 ± 88 pmol/kg/24 h (smokers, *n* = 23) 1.95 ± 0.40 µmol/mol creatinine (smokers, *n* = 23) 19.0 ± 6.8 nmol/24 h (passive smokers, *n* = 22) 266 ± 93 pmol/kg/24 h (passive smokers, *n* = 22) 1.57 ± 0.41 µmol/mol creatinine (passive smokers, *n* = 22) 20.5 ± 7.3 nmol/24 h (non-smokers, *n* = 23) 272 ± 79 pmol/kg/24 h (non-smokers, *n* = 23) 1.67 ± 0.57 µmol/mol creatinine (non-smokers, *n* = 23)	Pilger et al. (2001)
BTX	≤ 39 40–54 ≥ 55	Urine	HPLC-EC	1.44 ± 0.56 µmol/mol creatinine (*n* = 21) 1.13 ± 0.30 µmol/mol creatinine (*n* = 22) 1.52 ± 0.52 µmol/mol creatinine (*n* = 22)	Lagorio et al. (1994)
	21 av.	Lymphocytes	HPLC-EC	29.89 ± 3.28/10^5 dG (*n* = 28, 424.4 ± 181.7 mg/m^3 benzene) 26.12 ± 2.23/10^5 dG (*n* = 24, 103.3 ± 50.3 mg/m^3 benzene) 4.67 ± 3.44/10^5 dG (*n* = 35, 2.5 ± 2.4 mg/m^3 benzene) 3.74 ± 1.62/10^5 dG (*n* = 30, unexposed controls)	Liu et al. (1996)
Benzene	20–53	Urine	HPLC-EC	0.72 µmol/mol creatinine (*n* = 30, pre-shift) 0.75 µmol/mol creatinine (*n* = 30, post-shift) 0.99 µmol/mol creatinine (*n* = 30, late evening) 0.90 µmol/mol creatinine (*n* = 30, next morning)	Nilsson et al. (1996)
	19–57			0.85 µmol/mol creatinine (*n* = 32, unexposed controls)	
Styrene	41.5 ± 11.5 40.9 ± 13.1	Leukocytes	HPLC-EC	2.23 ± 0.54/10^5 dG (exposed workers, *n* = 17) 1.52 ± 0.45/10^5 dG (controls, *n* = 67)	Marczynski et al. (1997)
Asbestos		Urine	HPLC-EC	1.41 ± 0.56 µmol/mol creatinine (exposed smokers, *n* = 21) 1.38 ± 0.58 µmol/mol creatinine (exposed non-smokers, *n* = 9) 1.13 ± 0.45 µmol/mol creatinine (controls, smokers, *n* = 20) 1.01 ± 0.38 µmol/mol creatinine (controls, non-smokers, *n* = 21)	Tagesson et al. (1993)
	66–75 62–81	Leukocytes	HPLC-EC	1.00 ± 0.17/10^5 dG (asbestos patients, *n* = 7) 1.03 ± 0.20/10^5 dG (controls, *n* = 6)	Hanaoka et al. (1993)
	54.9 ± 4.3	Leukocytes	HPLC-EC	2.58 ± 1.33/10^5 dG (exposed, definite, *n* = 10)	Takahashi et al. (1997)

Table 1. (Continued)

Exposure	Age (year)	Sample	Assay	Mean ± SD or median	Reference
	55.3 ± 4.5			2.21 ± 1.32/10^5 dG (exposed, suspected, *n* =10)	
	54.3 ± 4.5			1.78 ± 1.46/10^5 dG (controls, *n* = 19)	
	53–70	Leukocytes	HPLC-EC	2.61 ± 0.91/10^5 dG (exposed 1994/95, *n* = 496)	Marczynski et al. (2000a)
				2.96 ± 1.10/10^5 dG (exposed 1995/96, *n* = 437)	
				2.55 ± 0.56/10^5 dG (exposed 1996/97, *n* = 447)	
	18–75			1.52 ± 0.39/10^5 dG (controls 1994–1997, *n* = 214)	
Silica	46.5 ± 2.1	Lymphocytes	HPLC-EC	2.61 ± 0.44/10^5 dG (miners with pneumoconiosis, *n* = 8)	Schins et al. (1995)
	46.6 ± 0.9			2.96 ± 0.34/10^5 dG (reference miners, *n* = 30)	
	50.7 ± 1.1			1.67 ± 0.27/10^5 dG (controls, *n* = 24)	
	62 ± 7	Leukocytes	HPLC-EC	2.51 ± 1.36/10^5 dG (silicotics, *n* = 42)	Pilger et al. (2000)
		Urine		1.99 ± 0.94 µmol/mol creatinine (silicotics, *n* = 42)	
	50 ± 6			3.20 ± 2.25/10^5 dG (exposed workers, *n* = 63)	
				2.28 ± 0.92 µmol/mol creatinine (exposed workers, *n* = 63)	
Cr	36.5 ± 12.7	Urine	HPLC-EC	1149.5 ± 759.5 pmol/kg (exposed workers, *n* = 48)	Kuo et al. (2003)
	31.0 ± 5.7			730.2 ± 377.6 pmol/kg (controls, *n* = 19)	
Cr, As	10–12	Urine	ELISA	15.5 ± 1.3 (± SE) ng/mg creatinine	Wong et al. (2005)
				(*n* = 71, Cr ≥ 2 µg/g creatinine)	
				11.6 ± 0.6 (± SE) ng/mg creatinine	
				(*n* = 71, Cr < 2 µg/g creatinine)	
				14.8 ± 1.1 (± SE) ng/mg creatinine	
				(*n* = 71, As ≥ 7.7 µg/g creatinine)	
				12.4 ± 0.9 (± SE) ng/mg creatinine	
				(*n* = 71, As < 7.7 µg/g creatinine)	
Co	38.5 ± 7.7	Urine	HPLC-EC	1.52 ± 1.69 µmol/mol creatinine (exposed, Co, *n* = 24)	De Boeck et al. (2000)
	40.7 ± 12.4			1.63 ± 1.42 µmol/mol creatinine	
				(exposed, hard metals, *n* = 29)	
	38.0 ± 8.8			1.46 ± 1.48 µmol/mol creatinine (controls, *n* = 27)	
Co, Cr	57.4 ± 9.6	Urine	HPLC-EC	1.15 µmol/mol creatinine (median, implants 3-4y, *n* = 23)	Pilger et al. (2002b)
	59.1 ± 7.5			0.75 µmol/mol creatinine (median, implants 1-2y, *n* = 23)	

Table 1. (Continued)

Exposure	Age (year)	Sample	Assay	Mean ± SD or median	Reference
$PM_{2.5}$	20–33	Lymphocytes	HPLC-EC	$0.55/10^5$ dG (autumn, $n = 40$) $0.27/10^5$ dG (winter, $n = 26$) $0.62/10^5$ dG (spring, $n = 38$) $0.58/10^5$ dG (summer, $n = 17$)	Sørensen et al. (2003)
		Urine		0.26 nmol/kg (autumn, $n = 49$) 0.22 nmol/kg (winter, $n = 49$) 0.24 nmol/kg (spring, $n = 47$) 0.21 nmol/kg (summer, $n = 47$)	
	45.5 ± 12.0	Urine	ELISA	13.26 ± 1.04 (± SE) µg/g creatinine (pre-workshift, $n = 91$) 15.22 ± 0.99 (± SE) µg/g creatinine (post-workshift, $n = 91$)	Kim et al. (2004)
	20–33	Lymphocytes	HPLC-EC	$0.58/10^5$ dG (17 students, summer) $0.55/10^5$ dG (35 students, autumn)	Sørensen et al. (2005)
		Urine		0.22 nmol/kg (46 students, summer) 0.26 nmol/kg (44 students, autumn)	
Glasswork		Urine	HPLC-EC	13.4 ± 6.1 nmol/l (exposed male workers, $n = 181$) 11.5 ± 6.1 nmol/l (exposed female workers, $n = 18$) 11.8 ± 5.7 nmol/l (unexposed male workers, $n = 49$) 10.1 ± 4.6 nmol/l (unexposed female workers, $n = 95$)	Tagesson et al. (1996)
PAHs	27–60	Urine	HPLC-EC	1.54 ± 0.96 nmol/mmol creatinine (bus drivers, rural, $n = 20$) 1.74 ± 0.87 nmol/mmol creatinine (bus drivers, city, $n = 29$)	Autrup et al. (1999)
	20–60			2.25 ± 1.13 nmol/mmol creatinine (postal workers, $n = 82$)	
		Urine	HPLC	3.3 ± 1.9 µg/g creatinine (controls, start of week, $n = 12$) 3.5 ± 1.7 µg/g creatinine (controls, end of week, $n = 12$) 2.6 ± 0.8 µg/g creatinine (roofers, asphalt fume, start, $n = 7$) 2.5 ± 0.8 µg/g creatinine (roofers, asphalt fume, end, $n = 7$) 2.5 ± 1.7 µg/g creatinine (roofers, coal-tar, start, $n = 19$) 3.0 ± 1.7 µg/g creatinine (roofers, coal tar, end, $n = 19$)	Toraason et al. (2001)
		Leukocytes		$1.96 \pm 0.83/10^5$ dG (controls, start of week, $n = 12$) $1.96 \pm 0.83/10^5$ dG (controls, end of week, $n = 12$)	

Table 1. (Continued)

Exposure	Age (year)	Sample	Assay	Mean ± SD or median	Reference
				1.24 ± 0.70/10^5 dG (roofers, asphalt fume, start, n = 6)	
				1.57 ± 1.65/10^5 dG (roofers, asphalt fume, end, n = 4)	
				1.03 ± 0.71/10^5 dG (roofers, coal-tar, start, n = 18)	
				0.56 ± 0.24/10^5 dG (roofers, coal-tar, end, n =18)	
	22–54	Leukocytes	HPLC-EC	0.72 ± 0.13/10^5 dG (coke-oven plant, n = 20)	Marczynski et al. (2002)
	22–58			1.12 ± 0.29/10^5 dG (graphite-electrode plant, n = 30)	
	23–58			0.52 ± 0.17/10^5 dG (controls, n = 47)	
	25.8 ± 4.7	Leukocytes	HPLC-EC	2.86 ± 1.39/10^5 dG (smokers, n = 56)	Kim et al. (2003)
	25.7 ± 6.2			2.72 ± 1.36/10^5 dG (non-smokers, n = 49)	
	38 ± 7	Leukocytes	HPLC-EC	4.31/10^5 dG (coke-oven workers, bottom, n = 40)	Zhang et al. (2003)
	39 ± 8			3.08/10^5 dG (coke-oven workers, middle, n = 41)	
	39 ± 8			3.07/10^5 dG (coke-oven workers, top, n = 38)	
	39 ± 8			3.42/10^5 dG (controls, n = 37)	
	25–67	Urine	LC-MS-MS	7.58 ± 4.53 ng/mg creatinine (coke-oven workers, n = 91)	Hu et al. (2004)
	32–58			5.59 ± 3.34 ng/mg creatinine (controls, n = 49)	
			ELISA	14.92 ± 9.33 ng/mg creatinine (coke-oven workers, n = 91)	
				14.69 ± 12.84 ng/mg creatinine (controls, n = 49)	
	21–53	Urine	HPLC-EC	23.3 nmo/l (engine room personnel, oil on skin, n = 19)	Nilsson et al. (2004)
	17–52			18.7 nmol/l (engine room personnel, no oil on skin, n = 15)	
	23–59			18.0 nmol/l (unexposed controls, n = 33)	

BTX Benzene, toluene, xylenes, *Cr* chromium, *As* arsenic, *Co* cobalt, $PM_{2.5}$ particulate matter ≤ 2.5 μm, *PAs* polycyclic aromatic hydrocarbons

filling station attendants exposed to benzene as well as in workers from asbestos, rubber and azo-dye industries no influence of smoking on the urinary excretion of 8-OHdG was found (Lagorio et al. 1994; Tagesson et al. 1993). In industrial art glass workers a significant effect of smoking on 8-OHdG excretion was found only among females (Tagesson et al. 1996).

Benzene, toluene, styrene and xylenes

On the basis that oxidative processes might be involved in the mechanisms of benzene toxicity, Lagorio et al. (1994) measured urinary 8-OHdG in 65 filling station attendants. Personal sampling on about seven time-points throughout a year was used to assess the exposure to benzene, toluene and xylenes. The authors reported a significant correlation between urinary 8-OHdG and the average yearly exposure to benzene. In contrast, exposures to toluene and xylenes, although highly correlating with the benzene level, were not found to affect the urinary concentration of 8-OHdG. The limitations of this study are related to the assessment of exposure, which was not derived from biomonitoring data, and to the possibility that other constituents of gasoline may cause oxidative DNA damage.

Liu et al. (1996) provided a direct evidence for the influence of benzene exposure on oxidative DNA damage. To test the possible association of internal benzene exposure with the formation of 8-OHdG in DNA, they included the measurement of urinary trans, transmuconic acid (TTMA) in a study on 87 benzene exposed workers. Both parameters, air benzene and TTMA, showed a significant correlation with 8-OHdG in lymphocyte DNA. There was also a good correlation between 8-OHdG and micronucleus frequency. Female workers showed significantly higher levels of 8-OHdG than male workers when exposed to the same concentration of air benzene, whereas no significant difference in lymphocyte 8-OHdG between female and male healthy controls was observed. Air toluene was found to show negative correlation with TTMA, 8-OHdG and micronucleus formation, which indicates that toluene might inhibit the metabolism and the genotoxicity of benzene. In workers with low exposure to benzene (2.46 mg/m^3) no increase in 8-OHdG was found as compared to controls.

Nilsson et al. (1996) found equal levels of urinary 8-OHdG in 30 benzene exposed workers and controls. However, 8-OHdG in late-evening urine from exposed workers was significantly increased over pre-shift values. Unfortunately, the authors did not use the same time schedule for the sampling in the control group, which makes it difficult to decide whether the elevated late-evening 8-OHdG was an exposure-related effect. Nevertheless, regression analysis resulted in a significant correlation between benzene exposure and 8-OHdG during the shift.

Based on their observation that styrene-7,8-oxide exposure in blood induces high molecular weight DNA fragmentation possibly due to oxidative stress, Marczynski et al. (1997) investigated the ability of styrene exposure to elevate 8-OHdG in white blood cells of 17 boatbuilders occupationally exposed to styrene. A significant increase in 8-OHdG was found in the styrene exposed group as compared to controls, but no evidence could be provided that styrene exposure > 10 years is more effective in producing oxidative DNA damage than short time exposure.

Asbestos

Various types of asbestos fibers induce 8-OHdG when incubated in vitro with DNA in the presence of hydrogen peroxide (Kasai and Nishimura 1984). Tagesson et al. (1993) found a significantly higher urinary excretion of 8-OHdG in 30 asbestos exposed workers as compared to 41 controls. Hanaoka et al. (1993) measured 8-OHdG in peripheral blood cells of asbestosis patients, observing no significant difference in the level of 8-OHdG between patients and controls without asbestos exposure. Therefore, the authors concluded that 8-OHdG is not a sensitive marker for past asbestos exposure at low levels. In contrast, Takahashi et al. (1997) could demonstrate a positive correlation between 8-OHdG in leukocyte DNA and incremental grades of asbestosis. In this study 8-OHdG showed also a positive correlation with the cumulative exposure to asbestos. Marczynski et al. (2000a) conducted a study on 496 asbestos-exposed workers in order to determine whether asbestos induces the formation of 8-OHdG in white blood cells. The data of this study point to a 1.7- to 2-fold increase in 8-OHdG due to asbestos exposure. However, no correlation was found between 8-OHdG and possible determinants, such as the duration of asbestos exposure, cumulative fibrous dust dose, asbestos-related diseases, age, smoking status, acute febrile infections, and intake of medicines, aspirin, calcium, magnesium, hormones and vitamines (Marczynski et al. 2000b). This supports the view that inhalation of asbestos is the causal factor for the observed differences in the level of 8-OHdG between asbestos workers and controls.

Silica

Exposure to silica has often been associated with the development of fibrotic lung disease, and silica has been designated as a carcinogen. Schins et al. (1995) measured 8-OHdG in peripheral blood lymphocytes of 38 retired coal workers, eight of them showing coal workers' pneumoconiosis. The levels of 8-OHdG in the miners were significantly higher than in the non-exposed controls. However, 8-OHdG in lymphocytes did not differ between miners with coal workers' pneumoconiosis and miners without coal workers' pneumoconiosis. In this study no association between 8-OHdG and the individual cumulative dust exposure was found, nor was there a synergistic effect between smoking and occupational exposure.

Pilger et al. (2000) determined urinary 8-OHdG and 8-OHdG in leukocyte DNA of 63 workers occupationally exposed to quartz and 42 patients with silicosis. No significant differences in 8-OHdG between healthy workers and silicosis patients were observed. Interestingly, in case of silicosis, urinary 8-OHdG correlated positively, whereas 8-OHdG in leukocytes correlated negatively with the forced expiratory volume in 1 s and the forced vital capacity. In the subgroup of silicosis patients with leukocytic 8-OHdG above the median level of all patients, a significantly lower urinary excretion of 8-OHdG was found as compared to the corresponding group of healthy workers. From these data the authors concluded that a less effective repair of 8-OHdG may be associated with a higher degree of pulmonary airway obstruction in patients with silicosis. Although no quantification of dust exposure was included in this study, workers with a personally estimated high dust exposure showed higher levels of 8-OHdG in leukocytes than did workers with a moderate dust exposure.

Chromium and cobalt

Hexavalent chromium is an established carcinogenic agent that has been shown to induce the formation 8-OHdG and FPG-dependent DNA strand breaks in human white blood cells in vitro (Lee et al. 2004, 2005). Substantial interindividual variation in the level of sodium dichromate-mediated oxidative DNA damage was found in vitro when analyzing white blood cells from 72 healthy adults by the FPG-comet assay. These differences in DNA strand breaks introduced by FPG have been suggested to be due to Cys^{326} variants of the human OGG1 gene (Lee et al. 2005). Urinary concentrations of 8-OHdG in 48 electroplating workers were higher than those in 19 healthy controls. In addition, a statistically significant positive correlation ($r = 0.44$, $P < 0.5$) between the urinary concentrations of chromium (μg/g creatinine) and 8-OHdG (nM/kg) was observed (Kuo et al. 2003). However, when relating the urinary concentration of 8-OHdG to that of creatinine, no significant difference in the levels of 8-OHdG between exposed workers and controls could be demonstrated in this study. Recently, Sørensen et al. (2005) found a significant association of $PM_{2.5}$ bound chromium and vanadium with lymphocyte 8-OHdG in 49 students who have been monitored for $PM_{2.5}$ exposure with portable equipment. By contrast, chromium and vanadium in personal samples of $PM_{2.5}$ were not associated with urinary 8-OHdG. In a recent cross-sectional study, children with urinary chromium concentrations > 2.2 μg/g creatinine showed higher urinary 8-OHdG levels (15.5 ± 1.3 ng/mg creatinine, $n = 71$) than did those with urinary chromium < 2.2 μg/g creatinine (11.6 ± 0.6 ng/mg creatinine, $n = 71$) (Wong et al. 2005).

Since cobalt has similar chemical properties to iron, there is reason to suppose Fenton like mechanisms for the production of ROS by cobalt. In human diploid fibroblasts, exposure to cobalt(II) in vitro (0–50 μM) caused an increase in 8-OHdG from 1.4 ± 0.4 to 2.2 ± 0.7 residues/10^5 dG ($n = 3$). Higher concentrations of cobalt(II) up to 250 μM, however, did not further elevate the level of 8-OHdG in DNA of fibroblasts (Ivancsits et al. 2002). In 24 male workers exposed to cobalt dusts no significant increase in urinary 8-OHdG was detected as compared to 27 control subjects (1.52 ± 1.69 μmol/mol creatinine and 1.46 μmol ± 1.48 μmol/mol creatinine, respectively) (De Boeck et al. 2000). In a study on the effect of internal exposure to cobalt and chromium on the excretion of 8-OHdG, 16 out of 46 patients with total hip replacements had blood levels of cobalt above 5 μg/l, which indicated a considerable release of cobalt from the used implants. However, no increase in urinary 8-OHdG could be demonstrated in these patients (Pilger et al. 2002b). Contrary to these findings, Hengstler et al. (2003) reported a decreased repair activity for 8-oxoguanine at exposure to cobalt > 4 μg/m^3 in the air. In addition, the repair activity for 8-oxoguanine correlated negatively with levels of DNA strand breaks in mononuclear blood cells. Recently, Mateuca et al. (2005) reported that urinary 8-OHdG in 73 workers exposed to cobalt containing dusts was positively influenced by the interaction between smoking and dust exposure.

Fine particulate matter

Fine particulate matter (< 2.5 μm) can cause the formation of 8-OHdG in the presence of hydrogen peroxide in vitro (Shi et al. 2003). Kim et al. (2004) investigated the urinary excretion of 8-OHdG in twenty boilermakers exposed to fine particulates. The relevant exposure consisted of residual oil fly ash and metal fumes. The subjects were monitored during a 5-day work period. The mean urinary concentrations of 8-OHdG were found to be significantly lower for each pre-workshift sample as compared to the corresponding post-workshift sample. In addition, a significant correlation between $PM_{2.5}$ 8-hr-time weighted average concentration and urinary 8-OHdG was derived, indicating an increase in 8-OHdG of 1.68 μg/g creatinine each 1 mg/m^3 $PM_{2.5}$ exposure. $PM_{2.5}$ vanadium, manganese, nickel and lead concentrations also showed significant correlation with urinary 8-OHdG, whereas $PM_{2.5}$ chromium exposure was only marginally associated with urinary 8-OHdG. Smoking was not found to modulate the association between urinary 8-OHdG and total $PM_{2.5}$ concentrations, whereas chronic bronchitis could be identified as a significant predictor of 8-OHdG in these workers. Personal exposure to $PM_{2.5}$ was found to be a predictor of 8-OHdG in lymphocyte DNA with an 11 % increase of 8-OHdG per μg/m^3 increase in personal $PM_{2.5}$ exposure (Sørensen et al. 2003). This relationship was assessed over 48 h in 68 subjects. To account for seasonal variation, the measurements were repeated four times in one year. Interestingly, no correlation between 8-OHdG in DNA, urinary 8-OHdG and FPG-sensitive sites was observed in this study.

Polycyclic aromatic hydrocarbons

Epidemiological studies have shown an increase in cancer incidence among workers exposed to Polycyclic aromatic hydrocarbons (PAHs). Autrup et al. (1999) compared carcinogen-DNA adduct levels with other exposure markers in 107 healthy bus drivers and 102 mail carriers. A significant positive correlation between urinary 8-OHdG and the level of benzo[a]pyrene bound to serum albumin was observed, and a negative correlation between 8-OHdG and the level of 2-amino-adipic semialdehyde was found. However, no association of 8-OHdG in urine with DNA adducts and malondialdehyde in plasma was found, and there was no difference in the mean levels of 8-OHdG between busdrivers working in the city center and in suburban or semirural areas.

Toraason et al. (2001) monitored urinary 8-OHdG and leukocyte 8-OHdG in 26 roofers exposed to coal-tar pitch dust and/or asphalt fume. No significant difference between start-of-week and end-of week values of urinary 8-OHdG was evident in asphalt roofers or controls. In addition, there was no significant difference in urinary 8-OHdG between asphalt roofers and controls. Although there was no significant difference in the urinary 8-OHdG excretion between controls and coal-tar exposed roofers, end-of-week urinary 8-OHdG in the latter was significantly elevated over start-of-week values. In contrast, end-of-week leukocyte 8-OHdG values in coal-tar exposed workers were significantly decreased as compared with start-of-week values. The authors interpreted this as an induction of repair mechanisms by coal-tar exposure that decreases the steady state level of oxidative DNA damage.

Marczynski et al. (2002) determined 8-OHdG in white blood cells of coke-oven workers and graphiteelectrode-producing plant workers exposed to PAHs. Clearly elevated levels of 8-OHdG in white blood cells of PAH-exposed workers were measured together with an increased frequency of DNA strand breaks. However, no association between the PAH metabolite 1-hydroxypyrene in urine and 8-OHdG could be demonstrated. In addition, no correlation of 8-OHdG with either benzo[a]pyrene concentrations or the sum of 16 PAH levels in the air at work place could be established.

Kim et al. (2003) used urinary 1-hydroxypyrene, 2-naphthol and leukocyte 8-OHdG to investigate the association between environmental PAH exposure and oxidative stress in 105 healthy Korean males without occupational PAH exposure. A significant correlation between urinary 1-hydroxypyrene and the 8-OHdG level in leukocytes could be observed, whereas urinary 2-naphthol correlated positively with 8-OHdG only in non-smokers and in subjects with GSTM1 null-type.

A study on 119 coke-oven workers could not confirm an association between leukocyte 8-OHdG and urinary 1-hydroxypyrene (Zhang et al. 2003). A marginally significant positive correlation was found between 8-OHdG and leukocyte aromatic DNA adducts. It is noteworthy that the urinary concentrations of 1-hydroxypyrene in this study were about 17- to 678-fold higher as compared to the concentrations of 1-hydroxypyrene in the unexposed subjects examined by Kim et al. (2003).

In contrast to the study of Zhang et al. (2003) a significant positive correlation between urinary 1-hydroxypyrene and urinary 8-OHdG was reported by Hu et al. (2004), who examined 91 workers in a coke oven plant. However, the results were dependent on the method used for the determination of 8-OHdG. Only the LC/MS/MS measurements of urinary 8-OHdG resulted in a significant difference between exposed workers and controls, whereas the ELISA method failed to uncover this difference.

Nilsson et al. (2004) reported an increased urinary excretion of 8-OHdG in engine room personnel (51 men) exposed to PAHs. The excretion of 8-OHdG was found to be highest among personnel who reported skin contact with oil. A highly significant correlation between urinary 8-OHdG and urinary 1-hydroxypyrene could be demonstrated. Recently, Marczynski et al. (2005) observed an increase in DNA strand breaks in 17 PAH-exposed workers who showed elevated concentrations of five hydroxyphenantrenes and two naphtalenes in urine after alteration of PAHs in the production material. This, however, was not associated with a significant increase in 8-OHdG in white blood cells of these workers, and no significant correlations of 8-OHdG with markers of external exposure and biomarkers of exposure were found.

Reliability of 8-OHdG as a biomarker of oxidative stress in humans

Despite considerable efforts to improve the analysis of 8-OHdG and to determine predictors of 8-OHdG formation, a number of questions concerning the occurrence of artifactual background and the environmental factors affecting the steady state level of

8-OHdG remain still unanswered (Collins et al. 2004). Some critical aspects related to the use of 8-OHdG in human biomonitoring studies are:

- The measurement of 8-OHdG remains, at least partly, an analytical challenge and the results strongly depend on the method used.
- Further investigation is needed to establish procedures that prevent artifactual oxidation of the DNA (Cadet et al. 1998).
- There are significant inter-laboratory differences in the base levels of 8-OHdG. Projects on the quality control of 8-OHdG assays (European Standards Committee on Oxidative DNA Damage) are still far away from a consensus on the level of oxidative damage in normal cellular DNA (ESCODD 2002).
- 8-OHdG is an unspecific marker, and a variety of confounding factors (e.g., age, gender, diet, smoking, alcohol consumption, physical activity, vitamin status) may affect the formation of 8-OHdG (Toraason et al. 1999; Chen et al. 1999; Bianchini et al. 2001). Beside this, the presence of 8-OHdG in DNA and urine may depend on other factors, such as DNA repair capacity (Gackowski et al. 2003; Cooke et al. 2005) or inflammatory reactions (Horiike et al. 2005).
- Effects of workplace exposures on the induction of 8-OHdG have been reported with controversial results.
- The formation or elimination of 8-OHdG may exhibit a considerable inter- and intraindividual variation (Pilger et al. 2001). Recently, levels of oxidative DNA damage ranging from 6.02 to 18.48 % were detected in white blood cells from 72 healthy donors by the FPG-modified comet assay (Lee et al. 2005). In addition, a substantial interindividual variation of FPG-induced DNA strand breaks in response to treatment of these cells with sodium dichromate was found, indicating differences in the accumulation of oxidative DNA damage.
- The interpretation of urinary 8-OHdG is not unequivocal. For example, an unchanged excretion of urinary 8-OHdG at increased oxidative burden does not rule out a decreased repair capacity and an accumulation of 8-OHdG in DNA (Poulsen et al. 1998). In addition, the contribution of the nucleotide pool to the concentration of 8-OHdG in urine is not clear.
- No significant correlation between urinary 8-OHdG and 8-OHdG in DNA could be demonstrated as yet (Foksinski et al. 2003)

Conclusion

8-OHdG is the most commonly measured marker of oxidative DNA damage. Many human biomonitoring studies have been performed in the last decade with the aim to investigate the influence of occupational and environmental exposures on the formation of 8-OHdG. However, there is still the problem with variable results and the lack of well established dose responses derived from human exposure. In addition, further work is needed to reach a consensus on the background level of 8-OHdG.

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