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ETHENO-DNA ADDUCTS AS OXIDATIVE STRESS-MARKERS IN CANCER ETIOLOGY AND CHEMOPREVENTION STUDIES

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Persistent cellular oxidative stress and enhanced lipid peroxidation (LPO) of PUFAs, leading to macromolecular damage and disruption of signaling pathways, are implicated in the development of human malignancies and other chronic degenerative diseases. LPO generates by oxidation of linoleic acid (LA) or arachidonic acid (ω-6 PUFAs) reactive aldehydes, such as *trans*-4-hydroxy-2-nonenal, which form etheno ε-DNA adducts in a variety of human tissues and thus can contribute to diet-related cancers. ε-Adducts are highly miscoding lesions in mammalian cells and can initiate/promote the carcinogenic process through specific point mutations (IARC Sci. Publ. N° 150, '99). Using validated ultrasensitive detection methods for these lead markers of oxidative stress-derived DNA damage (Nair et al., '95) we found highly variable background levels in tissues from 'unexposed' humans and rodents (Bartsch et al., '94). Levels were increased by several known risk cancer factors, e.g. excess metal storage, chronic inflammatory processes, overproduction of nitric oxide, or high ω-6 PUFA diet. We analyzed WBC-DNA from volunteers in a carefully controlled dietary study: High intake of ω-6 PUFA (> 35 g/day LA in sunflower oil) but not of oleic acid (OA) in rape seed oil increased the mean frequency of ε-DNA adducts in WBC 40 times in women but not in men (Nair et al., '97). Gavage of LA (but not of OA) to rats led to high levels of -adducts in WBC-DNA of females but to little increase in males (Nair et al., '01). We have now investigated in healthy women on a free diet (IARC-coordinated EPIC study, Heidelberg participants) correlations between dietary fatty acid intake (by questionnaire), LA- and OA-concentration in serum and ε-DNA adduct levels in WBC. ε-DNA adducts levels were not determined by LA intake alone, but depended on the ratio: ω-6 PUFA (LA) / monounsaturated fatty acids (OA) and of antioxidants consumed in the diet

(Hagenlocher et al., '01). Our results confirmed the protective effect of dietary vitamin E and vegetables against miscoding ε-DNA lesions in human surrogate cells, and indicated a marked gender difference in susceptibility, so far unexplained, towards such LPO-induced damage. Therefore, biomonitoring of ε-base adducts in WBC and urine (Nair '99) offers a tool to verify the efficacy of new antioxidants, e.g. those recently characterized in olive oil (Owen et al., '00). In part supported by Eu-contract ENV4-CT97-0505