tive substances are observed. The examples of use of amphiphilic polymer of *N*-vinylpyrrolidone as the carriers of low molecular weight and modificators of proteins are given. These polymers do not act on viscosity characteristics of blood and do not destroy erythrocytes.

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W14: Exogenous and Endogenous Background Exposures to Carcinogens and Regulatory Consequences

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Significance for risk assessment of increases in background levels of carcinogen-derived protein and DNA Aadducts

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Human DNA and protein are exposed continuously to many molecules capable of causing damage, derived from both exogenous and endogenous sources. These compounds may interact directly with the macromolecule to form adducts (genotoxic), or indirectly by generating reactive oxygen species (ROS), which cause oxidative damage. Analysis of DNA from healthy humans reveals many types of damaged 2′-deoxynucleosides, with oxidatively modified species predominating and accounting for at least 1 modified base/10^5 nucleotides. Typically, background levels of DNA adducts resulting from low molecular weight alkylating agents have been detected in the 1–10 adducts/10^7 nucleotide range. Background levels of amino acids alkylated by endogenous electrophiles are similarly seen in haemoglobin from control individuals. The default position currently taken by many regulatory bodies is that for genotoxic carcinogens the relationship between exposure and mutations or later biological effects has no threshold, i.e. any level of DNA adducts is considered to represent a carcinogenic risk. However if an endogenous damage-producing process is relatively active, it is possible that the excess biological effect associated with a low dose exogenous exposure to the same compound may not be detectable, i.e. an increase in mutation frequency cannot be seen over that of the untreated control species, and the endogenous process effectively defines the risk. There is consequently considerable current interest in the shapes of dose-response curves for biomarkers of exposure (such as DNA adducts) and effect in situations where the damage has both exogenous and endogenous causes, such as for example the case with ethylene oxide.

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Products of endogenous metabolism as cause of promutagenic DNA adducts

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The most prominent example of an endogenous compound producing DNA adducts is ethylene oxide, which is derived from endogenous ethylene. Ethylene is a normal body constituent; its endogenous formation is evidenced by exhalation in rats and in humans. The most abundant DNA adduct of ethylene oxide is 7-(2-hydroxyethyl)guanine (HOEtG). For a cancer risk assessment at low levels of DNA damage, exposure-related adducts must be discussed in relation to background DNA damage. In rats, subacute ethylene oxide exposures on the order of 1 ppm cause DNA adduct levels (HOEtG) of the same magnitude as produced by endogenous ethylene oxide. Endogenous background levels of HOEtG in DNA of humans are comparable to those that are produced in rodents by repetitive exogenous ethylene oxide exposures of about 10 ppm. A second topic to be highlighted is “etheno” DNA adducts, known to be formed from the carcinogen vinyl chloride, but also derived from endogenous sources. The major DNA adduct induced by vinyl chloride (approximately 98% of total adducts in rats), 7-(2-oxoethyl)guanine, is almost devoid of promutagenic activity. The clearly promutagenic “etheno” adducts N2,3-ethenoguanine and 3,N4-ethenocytosine each represent approximately 1% of the vinyl chloride DNA adducts in rats, and 1,N6-ethenoadenine is found at even lower concentrations. Etheno adducts have a long persistence and are repaired by glycosylases. Likely reasons for this background are oxidative stress and lipid peroxidation.

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Comparative biological activation of the endogenous carcinogen isoprene and chloroprene

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Buta-1,3-diene is *probably* carcinogenic in humans, with leukaemia being a significant risk from occupational exposures (IARC Group 1 carcinogen). The mono- and di-epoxides of butadiene are carcinogenic metabolite(s). Isoprene (2-methylbuta-1,3-diene) is the major endogenous hydrocarbon and so human exposures are unavoidable. However, isoprene is much less carcinogenic (ca. 100-fold) to mice and rats than butadiene. Studies of cancers among occupationally exposed workers, as well as animal experiments, led to the conclusions that isoprene is an animal carcinogen and *possibly* carcinogenic in humans (Group 2B). The metabolism of isoprene is similar to that of butadiene. Chloroprene (2-chlorobuta-1,3-diene) is a bulk industrial chemical that is *possibly* carcinogenic in humans (Group 2B). The metabolism of chloroprene is complex giving rise to a number of reactive metabolites: epoxides, chloro-aldehydes and chloro-ketones. The metabolite 1-(chloroethenyl)oxirane shows selectivity for G and C residues in DNA. Cytidine adducts are difficult to repair and this may be a mutagenic lesion. However, the reactive metabolites of chloroprene are efficiently scavenged by epoxide hydrolase and/or glutathione (S-transferase), therefore limiting the carcinogenic risk from these metabolites. The diene metabolites differ in their reactivities towards nucleophiles and there also differences in the ability of epoxide hydrolase and glutathione (S-transferase) to destroy these metabolites. All in all, the various factors conspire to make butadiene relatively more carcinogenic, whereas isoprene and chloroprene are less carcinogenic than might be anticipated.

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Sources and quantification of human backgroudexposure to acrylamide

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We elucidated human metabolism of acrylamide (AA) by applying labelled AA. Using a newly elaborated LC-ESI-MS/MS method we