the metal contaminations of all samples were measured chemically, and physico-chemical and microbial soil parameters (soil enzyme activities, soil biomass etc.) were determined. Our findings show that the MN frequencies increase in soils with identical composition as a function of their metal concentrations, whereas no correlations were seen between genotoxic effects and metal contaminations of soils from different sampling sites. The associations of physico-chemical parameters, genotoxic effects, and the activities of customarily measured soil enzymes are discussed.

O2-12 Translation elongation factor 1 delta sub-unit is a novel cadmium-responsive proto-oncogene

Pius Joseph, Yi-xiong Lei, Tong-man Ong. *Toxicology and Molecular Biology Branch, CDC/NIOSH, 1095 Willowdale Road, Morgantown, WV 26505, USA*

A large number of workers are potentially exposed to cadmium (Cd) in a variety of occupational settings. Cd has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen. However, little is known regarding the potential mechanisms of Cd carcinogenesis. Using BALB/c-3T3 cell transformation and nude mouse tumorigenesis models, we have investigated the molecular mechanism(s) responsible for cell transformation and tumorigenesis induced by Cd. Differential display analysis of gene expression revealed consistent and reproducible overexpression of a novel gene, translation elongation factor 1 delta sub-unit (TEF) in the transformed cells compared with the control, non-transformed cells. Similar overexpression of TEF was noticed in the cell lines developed from tumors grown in nude mice sub-cutaneously injected with the transformed cells. Nucleotide sequence analysis of the full-length cDNA (GenBank Accession Number AF304351) cloned from the transformed cells revealed an open reading frame encoding a predicted protein of 281 amino acids. A 31 KDa protein was detected in chinese hamster ovary cells and in monkey kidney COS7 cells transfected with an expression vector containing the entire coding region of TEF cDNA. Transfection of NIH3T3 cells with an expression vector containing the TEF cDNA resulted in its overexpression and this was associated with cell transformation as evidenced by the appearance of transformed foci. Taken together, these findings demonstrate that the cell transformation and tumorigenesis induced by Cd are due, at least in part, to the overexpression of TEF - a novel cellular proto-oncogene.

O2-13 The influence of bromate on biological key mechanisms

Tamara Grummt. *Federal Environmental Agency, Heinrich-Heine-Strasse 12, Bad Elster 08645, Germany*

The problem for legislators in establishing DBP standards is not only their diversity. The most important point is that they act by several different mechanisms.For bromate important hazard identification studies have already been done. The experiments with the DBP bromate described here were performed to examine key biological mechanisms at physiologically plausible concentrations.These mechanisms are cell proliferation, DNA repair alterations, apoptosis and mutagenicity. In addition we also studied the noncancer end point immunotoxicity, an underestimated area in hazard evaluation at low dose levels. The studies were carried out in primary lymphocytes cultures and in exfoliated epithelial cells.A small but significant depression in DNA repair capacity was observed. This depression was associated with a delay in cell division. Parallel to this finding an increase in the number of micronuclei in peripheral lymphocytes were scored. The differences were small and not statistically significant. Based on this results a following up-study for analysing the relationships between the cell-cycle regulation and DNA damage is currently in progress, because there is some evidence that chronic exposure to DBP-mixtures may be more potent than bromate alone.No prominent association was found between bromate exposure and the changes in immunotoxic parameters and apoptosis.Taking the results presented here together, bromate may be capable to modulate DNA repair via inhibitory effects. Several carcinogenesis studies have also indicated the critical role of DNA repair insufficiency in the process of carcinogenicity.

O2-14 2-Phenylbenzotriazoles are metabolically activated by human CYP1A1 and are capable of inducing CYP1A1

Yoshiyuki Yamazaki[1], Ken-ichi Fujita[1], Tetsuya Saito[1], Yoshiki Takahashi[1], Keiji Wakabayashi[2], Tetsuya Kamataki[1]. *[1]Laboratory of Drug Metabolism, Graduate School of Pharceutical Sciences, Hokkaido University, N12W6, Kita-ku, Sapporo 060-0812; [2]Cancer Prevention Division, National Cancer Center Research Institute, Japan*

2-Phenylbenzotriazoles (PBTAs) were isolated from river water as promutagens. These chemicals are metabolically activated by enzyme(s) present in rat liver S9 and show mutagenicity in the Ames test using *Salmonella typhimurium* TA98. However, it has not been clarified whether these chemicals are activated by human drug-metabolizing enzymes such as cytochrome P450 (CYP). Therefore, we examined the roles of human CYP in the mutagenic activation of PBTAs in the present study. The metabolic activation of PBTAs by human CYP was tested with eleven strains of *Salmonella typhimurium* TA1538 expressing each form of human CYP (CYP1A1, CYP1A2, CYP1B1, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 or CYP3A5) and NADPH-CYP reductase, established in our laboratory. Three PBTAs possessing different amino moieties bound to 4-position of benzene ring (-$N(C_2H_4OCH_3)_2$, -$N(C_2H_5)C_2H_4CN$ and -$N(C_2H_4OH)_2$) were employed. We found that these PBTAs were specifically activated by CYP1A1. Human CYP1A1 is not constitutively expressed in the liver, but is induced by polycyclic aromatic hydrocarbons (PAHs). Therefore, we examined whether PBTAs were capable of inducing CYP1A1 by using human hepatoma HepG2 cells, where CYP1A1 is induced by PAHs. HepG2 cells were incubated with a respective PBTA (0.1-1.0 μM). All PBTAs were found to induce the expression of CYP1A1 mRNA in a concentration-dependent manner. Thus, we conclude that PBTAs are specifically activated by human CYP1A1, and have the capacity to induce CYP1A1. PBTAs may be activated by CYP1A1 which are induced by PBTAs in humans.

O2-15 Detection and confirmation of mutagenicity in river water in Korea

Jung-Hwan Kwon[1], Hyun Kul Lee[2], Kyun Kim[2], Eunju Park[3], Myung-Hee Kang[3], Hye Sook Lee[4], Yong-Hwa Kim[2]. *[1]Toxicology Research Center, Korea Research Institute of Chemical technology(KRICT), P.O. Box 107, Yusong, Daejeon, Korea 305-600; [2]KRICT; [3]Department of Food and Nutrition, Hannam University, Daejeon, Korea*

It has been reported by several scientists in Korea that river waters exhibits mutagenicity by the Ames mutagenicity tests. However, most of the results were generated at one of the five major rivers and sampled at one particular time of the year. Therefore, it is not possible to figure out the implication of the mutagenicity in the water samples without the evidence of the temporal consistency of the activity, which results in the difficulty of identifying the causative agent, subsequently the difficulty of elimination/reduction procedures of the problematic agent from the environmental compartment.Using the Ames mutagenicity test with TA98 strain in the present study, we found a site at the Nakdong river near an industrial complex where a consistent mutagenicity was seen by sampling 5 times at one month interval in summer and fall seasons. The mutagenicity could be confirmed as positive using the comet assay and the 8-OH-deoxyG assay methods. Identification trial of the mutagen was undertaken by concentrating the material from river water using XAD-2 resin, desorbing with methanol and/or ethyl acetate and analyzing the material by HPLC, GC/MS, and proton NMR. Tentatively isolated and identified chemical from the water was 2-amino-6,7-dichlorobenzothiazole. However, the synthetic material does not show the Ames mutagenicity. We are currently searching the comutagenicity of the chemical and possible unknown mutagens in the isolated fraction.