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CELL DEATH INDUCED BY MOBILE PHONE EXPOSURE

The biological effects of man-made electromagnetic fields especially in the RF (radio-frequency) and ELF (extremely low frequency) regions of the spectrum, is a subject that has been of concern in the scientific community and the public during the last decades. The most powerful RF antennas in the proximate daily environment of modern man are handsets and base station antennas of cellular mobile telephony. In Europe the two systems of digital mobile telephony are Global System for Mobile Telecommunications (GSM) with a carrier frequency around 900 MHz and Digital Cellular System (DCS) referred also as GSM 1800 with a carrier frequency around 1800 MHz and same rest characteristics as GSM. Both systems use a pulse repetition frequency of 217 Hz. Thereby the signals of both systems combine RF and ELF frequencies.

RF and ELF electromagnetic fields have been reported to induce cell death in several *in vitro* studies. Additionally, in several *in vivo* studies mostly on mice and rats, DNA damage or apoptosis were found to be induced by ELF and RF magnetic fields. At the same time, several other studies do not find any connection between electromagnetic field exposure and DNA damage or apoptosis. Thus the reported results are contradictory and studies examining cell death induced by electromagnetic fields in the model biological system of *Drosophila* oogenesis have not been conducted until now.

The aim of the present study was to investigate whether GSM and DCS radiation can induce cell death during the early and mid stages of *Drosophila* oogenesis, where programmed cell death does not physiologically occur.

The Terminal Deoxynucleotide Transferase dUTP Nick End Labeling (TUNEL) assay was used to detect cell death (DNA fragmentation) in a biological model, the early and mid stages of oogenesis of the insect *Drosophila melanogaster.* The flies were exposed *in vivo* to either GSM 900-MHz or DCS 1800-MHz radiation from a common digital mobile phone, for a few minutes per day during the first 6 days of their adult life. The exposure conditions were similar to those to which a mobile phone user is exposed.

The experiments and the statistical analysis show that genomic DNA fragmentation of the egg chambers cells is induced by the mobile telephony radiation. Both types of radiation, GSM 900 MHz and DCS 1800 MHz induce cell death in a large number (up to 55% in relation to control) of ovarian egg chambers in the exposed insects with only 6 min exposure per day for a limited period of 6 days.

DNA fragmentation is induced in all cases predominantly at the two developmental stages named checkpoints, germarium and stages 7-8. Since the above checkpoints were already known to be the most sensitive stages in response to other stress factors such an observation, could be expected. The results show that these two checkpoints are the most sensitive stages also in response to electromagnetic stress.

The experiments show that in cases of electromagnetic stress induced by the GSM and DCS fields, the germarium checkpoint appears to be even more sensitive than the mid-oogenesis checkpoint at stages 7-8. Thus, the two checkpoints are not equally responsive to distinct types of stress and may therefore also respond differentially to other types of

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stress stimuli. A possible explanation for the more sensitive germarium stage is that it may be more effective in evolutionary terms for the animal to block development of any defective egg chamber at the beginning rather than at later stages, in order to prevent the waste of precious nutrients.

In conclusion, cell death was detected during all the developmental stages of early and mid oogenesis in *Drosophila,* from germarium to stage 10 and in all types of egg chamber cells (nurse cells, follicle cells, oocyte). Germarium and stages 7-8 were found to be the most sensitive stages in response to electromagnetic stress. However, the germarium checkpoint was found to be even more sensitive than stages 7-8 in response to this particular stress.

It is important to emphasize that the recorded effect in the oocyte, which undergoes meiosis during the last stages of oogenesis, may result in heritable mutations upon DNA-damage induction and repair, if not in cell death.

Source: Mutation Research, Vol. 626, Issue 1-2, January 2007.

A Study of Atmospheric Pollution at an Electronic Waste Recycling Site in Southeast China

The rapid race in technological development has led to a shortening of the useful life of electronic equipment such as TVs, PCs, fax machines and mobile phones. Discarded equipment ends up as electronic waste, or "e-waste" which is growing at an ever increasing rate.

Much of this e-waste from the US, Europe and other parts of the world finds its way into China every year. Guiyu town in southeast China has emerged as one of the major centers for e-waste processing. The processing is conducted without any health preventive measures with the result that a lot of potentially carcinogenic and hazardous substances are released into the atmosphere, threatening the health of workers and local residents.

The disposal, recycling and part salvaging of discarded electronic components have created different environmental problems.

The melting of circuit boards on a coal grill is a widely used method to obtain useful metals, which may generate chlorinated compounds, as well as heavy metals and metalloids in the air. Unsalvageable materials are disposed of either by dumping in the fields and rivers or by burning in open air. The uncontrolled combustion of electronic scraps has the potential to produce highly toxic heavy metals and metalloids, such as lead (Pb), cadmium (Cd), chromium (Cr), arsenic (As), as well as polyhalogenated pollutants, including polycyclic aromatic hydrocarbons (PAHs). Previous studies have shown the contamination of the terrestrial environment of Guiyu by persistent organic pollutants and heavy metals. PAHs are known to be persistent, bio-accumulative, carcinogenic and mutagenic. High levels of PAHs and heavy metals in air will impose serious environmental and biological problems. Increased risks of mortality and morbidity have been associated with elevated levels of total suspended particles (TSP) in ambient air, especially for fine particles with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$).

MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay is based on the ability of healthy cells to react with yellow MTT to form dark blue crystals. The number of viable cells is directly proportional to the amount of the crystals generated. The color can then be quantified by a multi-well scanning spectrophotometer.

There is currently limited information available on concentrations of PAHs and heavy metals in TSP and $PM_{2.5}$ produced by e-waste recycling, thus the main objectives of the present research study were to identify levels of atmospheric contamination, focusing on PAHs and toxic metals, of a recycling site in order to better understand its sources, and to conduct a preliminary cytotoxicity study of organic solvent extract of TSP and $PM_{2.5}$ using MTT assay.

Twenty-nine air samples of TSP (particles less than 30-60 μm) and thirty samples of particles with aerodynamic diameter smaller than 2.5 μm ($PM_{2.5}$) were collected at Guiyu from 16 August 2004 to 17 September 2004. The results showed that mass concentrations contained in TSP and $PM_{2.5}$ were 124+44.1 and 62.12+20.5 μg/m^3, respectively. The total sum of 16 USEPA PAHs associated with TSP and $PM_{2.5}$ ranged from 40.0 to 347 and 22.7 to 263 ng/m^3, respectively. Five-ring and six-ring PAHs accounted for 73% of total PAHs. The average concentration of benzo(a)pyrene was 2-6 times higher than in other Asian cities. Concentrations of Cr, Cu and Zn in $PM_{2.5}$ of Guiyu were 4-33 times higher than in other Asian countries. In general, there were significant correlations between concentrations of individual contaminants in TSP with $PM_{2.5}$ (i.e. PAHs, Cd, Cr, Cu, Pb, Zn, Mn except Ni and As). The high concentrations of both PAHs and heavy metals in the air of Guiyu may impose a serious environmental and health concern. Cytotoxicity of the extract of TSP and $PM_{2.5}$ of ten 24h samples collected against human promonocytic leukemia cell line U937 (ATCC 1593.2) was determined by the MTT cytotoxicity assay. The results showed that under the same concentrations of extract, $PM_{2.5}$ cytotoxicity was 2-4 times higher than TSP.

A more comprehensive investigation is needed to study the toxic effects of contaminants especially those associated with $PM_{2.5}$, emitted by the different operations of e-waste recycling.

Source: Atmospheric Environment, Vol. 40, Issue 36, November 2006.

EFFECTS OF LOW-DOSE GAMMA RADIATION ON DNA DAMAGE, CHROMOSOMAL ABERRATION AND EXPRESSION OF REPAIR GENES IN HUMAN BLOOD CELLS

Gamma radiation is well recognized as a potent carcinogen due to its potential of oxidative damage. It causes a variety of lesions in DNA including single- and double-strand breaks, DNA-protein cross-links, oxidized bases and abasic sites. Lesions induced in the DNA are subjected to cellular repair. Misrepair of DNA damage can lead to chromosomal aberrations, cell death, mutagenesis and carcinogenesis.

DNA repair plays a critical role in protecting normal individuals from the effects of radiation, including cancer. The DNA repair process is controlled by a specific set of genes encoding the enzymes that catalyze cellular responses to DNA damage. Loss of repair function, or alteration of the control of repair processes, can have very serious consequences for cells and individuals. Most oxidative DNA damage induced by gamma radiation is repaired by the base excision repair (BER) pathway. Defects in BER have been shown to result in hypersensitivity to ionizing radiation.

Radiation may alter the pattern of repair gene expression in such a way that BER genes may be up- or down-regulated. Changes in the expression of these genes can affect the ability of cells to repair DNA damage. A number of BER genes are responsible for the repair of free-radical-induced DNA damage that is produced by ionizing radiation. For example, *hOGG1* encodes the 8-oxoguanine-DNA-glycosylase which removes 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) opposite C and formamidopyrimidine (fapy) residues from DNA through the BER pathway. The alteration in *hOGG1* mRNA expression will affect the repair function for oxidized bases including 8-oxodG and fapy residues. *XRCC1* (X-ray repair cross-complementing gene 1) is a DNA repair gene involved in rejoining DNA strand breaks; therefore, the alteration in *XRCC1* mRNA expression would affect repair function for DNA strand breaks.

The biological and health effects from exposure to high doses of gamma radiation have been well documented. For example, excess cancer incidence, including leukemia, is the most important late effect of radiation exposure observed among atomic-bomb survivors.

However, exposure to low-dose gamma radiation is common in certain occupations but the biological and health effects from such exposure remain to be determined. The aim of this study was to investigate the effects of low-dose gamma radiation on DNA damage, chromosomal aberration and DNA repair gene expressions in whole blood and peripheral lymphocytes. The study revealed a dose-dependent effect of gamma radiation on DNA damage. Significant increases in DNA strand breaks and oxidative base damage, determined as formamidopyrimidine-DNA-glycosylase (FPG)-sensitive sites, were observed at absorbed doses of 5 and 10 cGy, respectively. However, gamma radiation at doses up to 500 cGy did not significantly increase the level of 8-oxodG determined by HPLC with electrochemical detection (HPLC-ECD). Gamma radiation as low as 5 cGy caused chromosomal aberrations determined as dicentric and deletion frequencies. This finding is significant since the genotoxic effects of gamma radiation can be observed even at a low dose of 5 cGy. Clearly, the effects on DNA strand breaks and FPG-sensitive sites in lymphocytes were higher than those in whole blood which indicated a higher sensitivity in lymphocytes. Therefore, lymphocytes may have certain benefits compared to whole blood for the *in vitro* detection of the effects of exposure to low doses of gamma radiation. Furthermore, gamma radiation decreased the mRNA expression of both *hOGG1* and *XRCC1* repair genes determined by reverse transcriptase-polymerase chain reaction (RT-PCR), with a significant decrease of expression being observed at 20 cGy. The expression levels of *hOGG1* and *XRCC1* mRNA were inversely correlated with the levels of FPG-sensitive sites and DNA strand breaks. The observation of decreased expression levels for *hOGG1* and *XRCC1* in gamma-irradiated lymphocytes has not been reported elsewhere.

These findings suggest that the genotoxic effects of gamma radiation may be due to a combination of DNA damage and reduced DNA repair capacity. It is well known that the biological and leukemogenic effects of ionizing radiation do not follow a linear dose-response but a quadratic dose-response pattern. Therefore, the findings may provide an explanation regarding significantly more biological and health problems than predicted by the linear dose-response relationship.

Source: International Journal of Hygiene Environmental Health, Vol. 209, No. 6, November 2006.

Exposure to Persistent Organic Pollutants and Hypertensive Disease

Persistent organic pollutants (POPs) are halogenated organic compounds that resist photochemical, biological, and chemical degradation. POPs include the "dirty dozen" [dioxins/furans, polychlorinated biphenyls (PCBs), and chlorinated pesticides], whose production and use is to end now that 59 nations ratified the United Nations' Stockholm Convention of 2001. While most of these chemicals have not been intentionally manufactured in developed countries for a number of years, they remain in the environment and are found in human blood and fat in almost everyone. Many bodies of water remain highly contaminated with these substances, and large amounts remain in hazardous waste sites.

Humans are generally exposed to POPs through their food supply. There is, however, recent evidence that suggests that inhalation is a more significant route of exposure than previously appreciated. While most POPs are not very volatile, they do volatize and can be transported and inhaled both in the vapor phase and bound to particulates. Air transport of contaminants can also result in contamination of food and produce.

The majority of POPs are known endocrine disruptors and many adversely affect the immune system. Human fetal exposure to PCBs is associated with neural and developmental changes, lower psychomotor scores, short-term memory and spatial learning effects, and long-term reduction of IQ. There is, however, a growing body of evidence that exposure to these compounds may also be associated with increased risk of chronic diseases that are not usually attributed to environmental factors, such as hypertension, ischemic heart disease, stroke, diabetes and chronic respiratory disease.

Thus, the present study was designed to test the hypothesis that living near a hazardous waste site containing POPs constitutes a risk of exposure (most likely primarily via inhalation) and consequently an increased risk for hypertension.

Researchers identified the zip codes of more than 800 waste sites contaminated with POPs and other pollutants, based on which zip codes of upstate New York were classified into three groups: "POPs sites", zip codes containing hazardous waste sites with POPs; "other waste sites", zip codes containing hazardous waste sites but not with POPs; and "clean sites", zip codes without any known hazardous waste sites. Age, gender, race, and zip code of residence of patients diagnosed with hypertension (ICD-9 codes 401-404) were identified using the New York Statewide Planning and Research Cooperative System (SPARCS) for the years 1993-2000. A generalized linear model, the negative binomial model, was used to assess the effect of living in a zip code with a hazardous waste site on the discharge rate of hypertension. After control for the aforementioned covariates, researchers found a statistically significant elevation of 19.2% (95% CI = 8.5%, 31%) in hypertension discharge rate for "POPs sites" and a 10% elevation in discharge rates for "other waste sites" as compared to "clean sites". In a subset of "POPs sites" where people have higher income, smoke less, exercise more and have healthier diets, there was still a 13.9% elevation of hypertension discharge rate as compared to "clean sites". The results support the hypothesis that living near hazardous waste sites, particularly sites containing POPs, may constitute a risk of exposure and of developing hypertension.

Further research involving direct exposure assessment and control for more individual risk factors is necessary for providing additional evidence for this hypothesis.

Source: Environmental Research, Vol. 102, Issue 1, September 2006.

OCCUPATIONAL LEAD EXPOSURE AND RISK OF PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurologic movement disorder in which neurons of the substantia nigra, which are responsible for dopamine production, attenuate in number or become functionally impaired. Resultant symptoms include resting tremor in the extremities and head, limb and/or trunk rigidity, bradykinesia, and postural instability. Although the primary cause of the destruction or failure of substantia nigra cells is unknown, mounting evidence exists for both environmental and genetic determinants. A growing body of evidence suggests that heavy metal cations stimulate free radical formation in the brain and can lead to neurodegeneration via peroxidative damage to the cell membrane. Increasing levels of heavy metal cations stimulate the conformational changes that can lead to fibrillation of recombinant α–synuclein. The aggregation and fibrillation of α–synuclein provoked by the presence of heavy metal cations could directly cause the intracellular protein inclusions that are observed in the substantia nigra of PD patients.

Although several studies have examined the relationship between blood lead (Pb) levels and environmental Pb exposure, results from blood Pb analysis are not noteworthy. Research into long-term or distant past Pb exposures is confounded by the body's ability to purge metals quickly from the blood stream. Because the half-life of Pb in blood is approximately 1 month, blood Pb levels only reveal if the individual has experienced a relatively current exposure to environmental Pb. Thus, blood Pb levels indicate only acute and recent exposures to Pb rather than representing a chronic and/or extended exposure history. Rather than within circulating blood, the main repository for chronic Pb stores in the body is within bone. Pb is stored in the bone by replacing calcium of the hydroxy-apatite crystals of the bone mineral. Through a continual process of bone remodeling, synthesis, and

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LONG-TERM EXPOSURE TO AIR POLLUTION: INCIDENCE OF CARDIOVASCULAR EVENTS IN WOMEN

Exposure to air pollution has been associated with death and hospitalization from cardiovascular causes. Uncertainty remains about the magnitude of these associations, the mechanisms, and the effects of long-term exposure to pollutants, as compared with short-term exposure. Although previous studies of daily increases in exposure to pollution have assessed both fatal and nonfatal events, studies investigating long-term exposure — estimating average exposure during years of follow-up — have evaluated mortality only on the basis of death certificates. The increase in mortality associated with long-term exposure to air pollution is larger than that seen in studies of short-term exposure, and long-term effects on death rates serve as the current basis for fiercely challenged environmental regulations in the United States.

In previous studies of the long-term effect of air pollution on cardiovascular disease, investigators have averaged exposures across a city and then compared health effects between cities. However, gradients of exposure to pollutants within cities also affect the risk of death from cardiovascular causes and may be associated with subclinical atherosclerosis.

Now a new study has evaluated long-term exposure to air pollution and the incidence of cardiovascular disease in the Women's Health Initiative (WHI) Observational Study, a prospective cohort study with medical-record review and classification procedures designed to document specific first cardiovascular events. The study also examined how between-city and within-city gradients of exposure to particulate matter of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) are associated with first cardiovascular events.

The WHI enrolled postmenopausal women between the ages of 50 and 79 years in the study from 1994 to 1998. All subjects lived within commuting distance of one of 49 WHI clinical centers and satellite clinics in 36 U.S. Metropolitan Statistical Areas (referred to throughout as "cities"). Eligible subjects were those who planned to remain in the area and were free from conditions (including alcoholism, mental illness, and dementia) that might have precluded their participation in follow-up surveys. Baseline questionnaires assessed demographic and lifestyle characteristics, cardiovascular risk factors, medical history, diet, and medications. Written informed consent was obtained from all subjects. Anthropometric and blood-pressure measurements were performed at baseline.

The study population was restricted to subjects without a history of physician-diagnosed cardiovascular disease, including previous myocardial infarction, congestive heart failure, coronary revascularization, and stroke. To establish a stable primary residence during follow-up, researchers included women who lived within 150 miles (241 km) of a clinic (and had not changed clinics) before either death or the year 2002. Institutional review boards at the University of Washington and the Fred Hutchinson Cancer Research Center approved the study.

Data on the monitoring of air pollution was obtained from the Environmental Protection Agency's Aerometric Information Retrieval System with the use of AirData. Such data are recorded for $PM_{2.5}$ and particulate matter of less than 10 μm in aerodynamic diameter (PM_{10}), sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone. Monitors were selected on the basis of monitoring objectives and scale to represent ambient community-scale exposure and excluded those with data available from less than 50% of intended samples. On the basis of a five-digit ZIP Code centroid, the nearest monitor to the location of each residence was identified and used to assign an average of annual pollutant concentrations to each study subject. Only women linked to a monitor within 30 miles (48 km) of their residence were included. The long-term average $PM_{2.5}$ concentration was the exposure of interest, and the annual average concentration in the year 2000 was the primary exposure measure, owing to the substantially increased network of monitors in place in that year, as compared with previous years.

Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia.

A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of $PM_{2.5}$ exposure varied from 3.4 to 28.3 μg/m^3 (mean, 13.5). Each increase of 10 μg/m^3 was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of $PM_{2.5}$ (hazard ratio, 1.35; 95% CI, 1.08 to 1.68).

This study provides further evidence of the association between long-term exposure to air pollution and the incidence of cardiovascular disease. It confirms previous reports and moreover indicates that the magnitude of health effects may be greater than previously recognized. The results suggest that efforts to limit long-term exposure to fine particles are warranted.

Source: New England Journal of Medicine, Vol. 356, No. 5, 2007.

Effect of Organophosphate Insecticides on Regions of the Developing Rat Brain

Organophosphates are undergoing increasing restrictions on their home use in the United States, but nonetheless they still account for more than 50% of all insecticide use. One of the major concerns for human health is the propensity of these agents to produce developmental neurotoxicity, even when exposures are too low to elicit signs of systemic intoxication. In that regard, chlorpyrifos has been the most studied organophosphate, and it is now clear that the original view of its mechanism of action—cholinesterase inhibition via its active metabolite, chlorpyrifos oxon—is insufficient to explain its ability to damage the developing brain. In fact, multiple mechanisms target neural cell replication and differentiation, axonogenesis and synaptogenesis, and the development and programming of synaptic activity, culminating in behavioral deficits.

In a recent study, researchers compared the dose-effect relationships for systemic toxicity and developmental neurotoxicity for chlorpyrifos, diazinon, and parathion. Although parathion exhibited the highest systemic toxicity, it was actually less neurotoxic toward neurite formation and development of cholinergic projections, whereas diazinon and chlorpyrifos were less systemically toxic and more neurotoxic.

Now in a new study this approach has been extended to the evaluation of serotonergic (5HT) systems in the neonatal rat brain.

Studies with chlorpyrifos show that 5HT systems are among the most sensitive to developmental disruption, with adverse effects detectable even when exposures lie below the threshold for inhibition of cholinesterase. Targeting of 5HT function is critical for three distinct reasons. First, 5HT is a morphogen in the developing mammalian central nervous system; perturbations of this system lead to errors in the architectural assembly of the brain. Second, disruption or enhancement of 5HT synaptic communication in early development permanently "programs" future 5HT function, so even greater neurobehavioral anomalies emerge later. Third, unlike the adverse effects on cholinergic systems, which typically involve cognitive deficits, alterations in 5HT function elicit changes in affective states, appetite, and sleep patterns, thus expanding the scope of behavioral end points that need to be considered after early organophosphate exposure.

The present study evaluated the immediate effects of neonatal treatment with doses of diazinon and parathion below the maximum tolerated dose and spanning the threshold for barely detectable cholinesterase inhibition.

Neonatal rats were exposed to daily doses of diazinon or parathion on postnatal days (PND)1-4 and an evaluation was made of 5HT receptors and the 5HT transporter in brainstem and forebrain on PND5, focusing on doses of each agent below the maximum tolerated dose.

The results showed that diazinon evoked up-regulation of $5HT_{1A}$ and $5HT_2$ receptor expression even at doses devoid of effects on cholinesterase activity, a pattern similar to that seen earlier for another organophosphate, chlorpyrifos. In contrast, parathion decreased $5HT_{1A}$ receptors, again at doses below those required for effects on cholinesterase. The two agents also differed in their effects on the 5HT transporter. Diazinon evoked a decrease in the brainstem and an increase in the forebrain, again similar to that seen for chlorpyrifos; this pattern is typical of damage of nerve terminals and reactive sprouting. Parathion had smaller, nonsignificant effects.

These results support the idea that, in the developing brain, the various organophosphates target specific neurotransmitter systems differently from each other and without the requirement for cholinesterase inhibition, their supposed common mechanism of action.

In fact, the 5HT system is especially vulnerable to disruption by diazinon, chlorpyrifos, and parathion, with parathion showing a distinctly different spectrum of actions from the other two agents. The fact that alterations in neurodevelopment occur with organophosphate exposures below the threshold for cholinesterase inhibition reinforces the inadequacy of this biomarker for assessing exposure or outcome related to developmental neurotoxicity. Finally, the differential effects of the various organophosphates raise the intriguing possibility that safer compounds could be engineered that avoid the critical mechanisms evoking developmental neurotoxicity.

Source: Environmental Health Perspectives, Vol. 114, No. 10, October 2006.

NEUROPSYCHOLOGICAL AND RENAL EFFECTS OF DENTAL AMALGAM IN CHILDREN

Although it is estimated that more than 70 million dental amalgam restorations are placed annually in the United States, the health risks posed by the potential chronic release of metallic mercury vapor from amalgams (40-50% mercury by weight) remain unclear. Occupational exposures resulting in urinary mercury levels greater than 50 µg/L have been associated with various neurological, renal, and immunological impairments. Potential effects of lower occupational levels of mercury have also been evaluated, but results are inconsistent. Studies of dentists have found urinary mercury levels as low as 4 to 10 µg/L to be inversely associated with scores on tests of neurobehavioral function, including memory, attention, motor coordination and steadiness, and mood, but others failed to confirm a statistically significant association between urinary mercury and neurobehavioral function among dentists.

For the most part, studies in the general adult population, which presume that exposure to metallic mercury is primarily a result of dental amalgams, have not found significant associations between neuropsychological function and various amalgam exposure indexes, including urinary mercury level (when measured, generally <5 µg/L), number of amalgam restorations, total number of amalgam surfaces, and number of occlusal amalgam surfaces. Some studies suggest that dental amalgams are associated with neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis. In other studies, interventions such as the administration of chelating agents or the removal of dental amalgam have failed to demonstrate health benefits. Caution is warranted in drawing inferences from the available data, however, insofar as none of the studies evaluating the health effects of dental amalgam were randomized clinical trials.

A larger concern is that few data are available on the possible effects of amalgam on children, who might be more vulnerable to mercury toxicities because of their developmental immaturity during the period in which the risk of caries is greatest, and thus the placement of amalgam is most frequent. Amalgam fillings in a child's mouth are associated with greater exposure to mercury, as determined by significantly higher urinary mercury levels. Whether the exposure levels that result from the placement of amalgam are sufficiently high to adversely affect children's health remains uncertain.

In view of this, The New England Children's Amalgam Trial (NECAT) was conducted as a randomized clinical trial comparing the health of children whose caries were restored using either dental amalgam or mercury-free composite materials.

A total of 534 children aged 6 to 10 years at baseline with no prior amalgam restorations and 2 or more

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reabsorption, Pb is released into the blood stream and circulates throughout the body. In the brain, Pb diffuses easily across the blood brain barrier and binds to sulphydryl groups, resulting in Pb neurotoxicity that leads the neurodegeneration via intracellular oxidative damage.

Additionally, while the half-life of Pb in blood is very short, the half-life of Pb in bone is measured in years and decades, depending on the type of bone [the hard bone of the tibia (half-life of approximately 20 years) releases Pb more slowly over time than the soft, spongy bone of the calcaneus (half-life of < 10 years)] and the individual's metabolic rate of leaching and clearance. Measuring Pb concentration in bone using K-shell X-ray fluorescence (K-XRF) provides a proxy for current whole-body Pb content, independent of whether the exposure is current. Because K-XRF measurements estimate the current level of blood stores in the body, they can be used to construct an indirect assessment of an individual's past exposures to Pb.

In a recent study to investigate the association between objective chronic occupational Pb exposure and the risk of PD, 121 PD patients and 414 age-, sex-, and race-, frequency-matched controls were enrolled in a case-control study. As an indicator of chronic Pb exposure, concentrations of tibial and calcaneal bone Pb stores were measured using ^{109}Cadmium excited K-XRF. As an indicator of recent exposure, blood Pb concentrations were measured. Occupational data were collected on participants from 18 years of age until the age of enrollment, and an industrial hygienist determined the duration and intensity of environmental Pb exposure. Physiologically based pharmacokinetic modeling was employed to combine these data and whole-body lifetime Pb exposures for each individual were estimated.

Logistic regression analysis produced estimates of PD risk by a quartile of lifetime Pb exposure which showed that risk of PD was elevated by more than 2-fold for individuals in the highest quartile for lifetime Pb exposure relative to the lowest quartile, adjusting for age, sex, race, smoking history, and coffee and alcohol consumption.

The present study provides additional objective evidence to support the hypothesis that long-term exposure to heavy metals, such as Pb, contributes to the accumulation of peroxidative damage and neurodegenerative cell death that is observed in PD.

Source: Environmental Health Perspectives, Vol. 114, No. 12, December 2006.

The 6th Princess Chulabhorn International Science Congress (PC VI)
November 25-29, 2007, Bangkok, THAILAND

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THE INTERFACE OF CHEMISTRY AND BIOLOGY IN THE "OMICS" ERA

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NEUROPSYCHOLOGICAL AND RENAL EFFECTS OF DENTAL AMALGAM IN CHILDREN

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posterior teeth with caries were randomly assigned to receive dental restoration of baseline and incident caries during a 5-year follow-up period using either amalgam (n=267) or resin composite (n=267) materials.

The primary neuropsychological outcome was 5-year change in full-scale IQ scores. Secondary outcomes included tests of memory and visuomotor ability. Renal glomerular function was measured by creatinine-adjusted albumin in urine.

Children had a mean of 15 tooth surfaces (median, 14) restored during the 5-year period (range, 0-55). Assignment to the amalgam group was associated with a significantly higher mean urinary mercury level (0.9 vs 0.6 µg/g of creatinine at year 5, *P<.001)*. After adjusting for randomization stratum and other covariates, no statistically significant differences were found between children in the amalgam and composite groups in 5-year change in full-scale IQ score (3.1 vs 2.1, *P*=.21). The difference in treatment group change scores was 1.0 (95% confidence interval, –0.6 to 2.5) full-scale IQ score point. No statistically significant differences were found for 4-year change in the general memory index (8.1 vs 7.2, *P=.34),* 4-year change in visuomotor composite (3.8 vs 3.7, *P=.93),* or year 5 urinary albumin (median, 7.5 vs 7.4 mg/g of creatinine, *P=.61).*

In this study, there were no statistically significant differences in adverse neuropsychological or renal effects observed over the 5-year period in children whose caries were restored using dental amalgam or composite materials. Although it is possible that very small IQ effects cannot be ruled out, these findings suggest that the health effects of amalgam restorations in children need not be the basis of treatment decisions when choosing restorative dental materials.

Source: JAMA, Vol. 295, No. 15, April 2006.

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