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# DEVELOPMENTAL EFFECTS OF MANGANESE IN DRINKING WATER IN SCHOOL-AGE CHILDREN

Manganese (Mn) is commonly found in groundwater because of the weathering and leaching of Mn-bearing minerals and rocks into the aquifers; concentrations can vary by several orders of magnitude. Because homeostatic mechanisms regulate Mn concentration in the organism, notably low absorption levels and a high rate of presystemic elimination by the liver, it is generally believed that the oral route poses no significant toxic risk. Moreover, exposure to Mn from water consumption has been of little concern, because the intake of Mn from ingestion of water is small compared with that from foods, except for infants.

Few data are available on the risks from exposure to Mn from drinking water. One study in adults and three studies in children suggest that high Mn levels in water can be neurotoxic. In the Chinese province of Shanxi, 92 children 11-13 years of age, exposed to 240-350 µg Mn/L in water, had elevated hair Mn concentration (MnH), impaired manual dexterity and speed, short-term memory, and visual identification when compared with children from a control area. In Bangladesh, higher Mn concentration in water (MnW) was significantly associated with lower intelligence quotient (IQ) in 142 children 10 years of age; the mean MnW was 800 µg/L. In Quebec (Canada), a pilot study on 46 children 6-15 years of age showed that those exposed to higher MnW had significantly higher MnH, and the latter was associated with teacher-reported hyperactive and oppositional behaviors. Two case reports show child Mn intoxication from water containing >1,000 µg Mn/L, one presenting with attention and memory impairments and the other with neurologic symptoms including a repetitive stuttered speech, poor balance, coordination, and fine motor skills.

Mn concentration in drinking water is not regulated in the United States or Canada. Health-based guidelines for the maximum level of Mn in drinking water are set at 300 µg/L by the U.S. Environmental Protection Agency (2004) and at 400 µg/L by the World Health Organization (2008).

The present study assesses the relationship between exposure to Mn from drinking water and IQ of school-age children living in communities relying on groundwater. In addition, it examines the relations between MnH and estimated Mn intakes from water consumption and from the diet.

The study was conducted as a cross-sectional study in southern Quebec between June 2007 and June 2009. Municipalities were considered as potential study sites if their aqueduct was supplied by groundwater. The purpose of the study was explained to principals and teachers of elementary schools in the selected study sites. Recruitment of children was restricted to those who had lived in the same house for over three months to ensure continuous exposure to the same source of water for this minimum time period; 362 children (age 6-13 years) participated in the study.

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## DEVELOPMENTAL EFFECTS OF MANGANESE IN DRINKING WATER IN SCHOOL-AGE CHILDREN

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Researchers engaged in the study collected a hair sample from the occiput of each child, cutting as close as possible to the root with surgical stainless steel scissors in order to assess MnH.

When MnH was examined as the prediction of IQ in adjusted analyses, it was significantly associated with lower full scale IQ scores but not performance or verbal IQ scores. In adjusted analyses, however, higher MnH was also associated with lower performance and verbal IQ scores.

The findings from the present study support the hypothesis that low-level, chronic exposures to Mn from drinking water is associated with significant intellectual impairments in children.

Because of the common occurrence of this metal in drinking water, the researchers believe that national and international guidelines for safe Mn in water should be reconsidered.

***Source:*** Environmental Health Perspectives, Vol. 119, Issue 1, Pages 138-143, January 2011.

# *Assessing the Impact of Petrol Stations on their Immediate Surroundings*

This study involves a novel methodology for evaluating the extent to which petrol stations affect their surroundings.

The method is based on the fact that the ratio of the concentrations of aliphatic and aromatic hydrocarbon pollutants in the air of the petrol stations and their surroundings (basically determined by vapor emissions from unburned gasoline) differs from the ratio found in urban air, which is mainly influenced by traffic emissions. Bearing this in mind, the spatial limit of influence of petrol stations in any direction would be the first point, moving away from the station, where the ratio becomes equal to the urban background ratio. Application of the methodology involves multipoint measuring campaigns of the air at the studied petrol station and built-up area in general and processing the data with software capable of providing isoconcentration contours.

The study was carried out in the city of Murcia, located in the south-east of the Iberian Peninsula, which is characterized by very low annual rain fall (around 375 $l/m^2$), annual average temperature of 18°C and extreme temperatures of 40-45°C in summer and -2-0°C in winter.

The air of the urban surface of the city, around 465 $hm^2$, was the subject of the study with regard to volatile organic compound (VOC) concentrations together with that of a petrol station known as “La Fica”. This petrol station is located on the east side of the city and is Stage I implemented, that is, it uses vapor recovery devices to return the VOC-saturated volume of air displaced from the storage tank being filled to the tank being emptied. It has four pumps for gasoline and diesel and one for motorbikes. The north and south approaches to the petrol station are unhindered due to the presence of a 30 m-wide road. A single low building is situated east of the station and has no more construction behind it. On the other side of the road (west of the station) stand several 3-storey blocks. This explains why this particular petrol station was chosen: the west area is inside the built-up area of the city, whereas the east is practically undeveloped.

As the traffic conditions in the city are not the same throughout the week, working days (from Monday 08.00 h to Friday 22.00 h) were distinguished from weekends (Friday 22.00 h to Monday 08.00 h). This study was carried out in two different Monday-to-Friday campaigns (from 26/05/08 to 30/05/08, and from 16/06/08 to 20/06/08) with a total exposure time in each campaign of 110 h.

Benzene, n-hexane and cyclohexane were the VOCs chosen for analysis during the two different Monday-to-Friday campaigns as these compounds are representative of aromatics, paraffins and cyclic paraffin hydrocarbons, respectively. Hydrocarbon desorption from the active charcoal in the passive samplers was carried out using carbon disulfide.

In both campaigns, lower impacts were obtained in those directions with heavy traffic density (west and south), whereas directions north and east, without buildings or roads, showed higher impacts. This can be explained as follows: when the petrol station is surrounded by roads with intense traffic, the emissions from the petrol station are not as important as those coming from vehicle combustion. If the petrol station emissions are mixing with relatively clean air the typical n-hexane/benzene ratio from these stations changes more slowly. From these results, it can be concluded that the influence of petrol stations is a relative question although, in no case, was the influence greater than 75 m. Presumably, small and medium sized petrol stations will have a similar impact on their surroundings as the one in this work; however, it is recommended that this methodology be applied to specify their reach with more precision. This methodology will help establish a “belt” around petrol stations where vulnerable populations and activities such as those in schools and hospitals should be restricted. Finally, it should be remembered that minimization of concentrations of chemicals of concern, regardless of their sources, is indispensable for effective health protection. For this purpose, similar or different methodologies should be applied or developed to assess the spatial limits of influence of these other sources.

***Source:*** Journal of Environmental Management, Vol. 91, Issue 12, Pages 2754-2762, December 2010.

# Effective Actions to Reduce Health Impacts of Air Pollution

Evidence from natural experiments and from analyses of long-term trends indicates that reducing air pollution has clear health benefits. Traditionally, air quality management has focused on emissions-based pollution control. Although regulations promoting cleaner vehicle engine technology, power production, and industrial combustion processes have clearly led to decreased emissions, increases in vehicle-kilometers traveled and overall power generation and industrial activity may offset their effectiveness. Interventions separating people from pollution, which reduce exposure independent of emissions controls and mitigate health impacts, have largely been overlooked as components of formal strategies. For example, land-use decisions typically do not consider air pollution-related health impacts and do not require minimum distances between sources and individuals. A consequence of this has been the siting of residences, schools, and hospitals near major traffic arteries. Modification of the infiltration of outdoor pollutants into indoor environments, which is largely a function of air exchange and building design, offers further opportunities for exposure reduction. Activity modification at an individual level such as altering the duration, intensity, and location where individuals are physically active can also help reduce air pollution exposure and dose. Because the benefits of exercise on health are well established, whereas the net consequences of physical activity in polluted environments remain unclear, recommendations on this topic must carefully weigh the benefits and risks of outdoor physical activity. To make further progress in reducing air pollution-related health impacts, a new framework is needed that incorporates strategies at regulatory, community, and individual levels, to reduce both emissions and exposures.

An international multidisciplinary workshop was convened to discuss evidence of the effectiveness of actions to reduce health impacts of air pollution at both the community and individual level. The overall aim was to summarize current knowledge regarding air pollution exposure and health impacts leading to public health recommendations.

During the workshop, experts reviewed the biological mechanisms of action of air pollution in the initiation and progression of disease, as well as the state of the science regarding community and individual-level interventions. The workshop highlighted strategies to reduce individual baseline risk of conditions associated with increased susceptibility to the effects of air pollution and the need to better understand the role of exposure duration in disease progression, reversal, and adaptation.

Further research is needed to document the effects of specific personal-level interventions on relevant clinical outcomes. For example, future research should consider long-term implications of exposure to air pollutants when determining the impact of diet and the impact of antioxidant supplementation, as well as the dose and duration of supplementation that would provide the greatest protective effect, in terms of clinically relevant outcomes.

Given the potential conflict between advice to reduce strenuous outdoor activity in order to avoid outdoor air pollution exposure, and the broader health benefits of physical activity, it is imperative to better understand the interaction of exercise and poor air quality on cardiorespiratory health and function in healthy, compromised, and athlete populations. Although the recommendation of remaining indoors during high outdoor pollution events is supported by exposure data, no data on direct health benefits exist. Further evaluation needs to be conducted in order to better advise individuals on appropriate exposure reduction strategies. Additionally, a better understanding of the relative toxicity of indoor- and outdoor-generated pollutants, and the role of copollutants, both indoors and outdoors, in producing health effects, is needed. Finally, implementing and assessing strategies at indoor locations where individuals spend a lot of time would be beneficial. For example, providing and assessing the effects of air conditioning at schools located along major roadways would be useful.

Regulatory interventions, which have been the primary focus of air quality management, are essential in reducing ambient pollutant levels and, consequently, health impacts among the public. To complement progress made through regulation, interventions implemented at the community and individual levels should also be given attention. Although there are some recent exceptions, such as California Senate Bill 352 regarding school locations in relation to roadways, land-use decisions typically do not consider air pollution-related health impacts.

Individual-level interventions that influence personal behaviors to modify pollutant exposure and/or dose are also potentially useful approaches to mitigate health effects of air pollution. Further, reducing individual baseline disease risk will mitigate air pollutant impacts on disease progression, whereas targeted interventions focused on diet, supplementation, and physical activity can reduce individual susceptibility to air pollution. Stressing individual-level interventions, however, raises the issues of burden of responsibility and environmental justice.

With this in mind, it is important to develop a new framework that approaches air quality and health from regulatory and community- and individual-level perspectives. Working within an evidence-based multidisciplinary public health framework and incorporating a stronger evidence base that addresses current knowledge gaps will allow us to move from good intentions to proven interventions.

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***Source:*** Environmental Health Perspectives, Vol. 119, No. 1, Pages 29-36, January 2011.

# Risk Factors for Cardiovascular Diseases Resulting from Long-term Air Pollution – A Study among the Elderly in Taiwan

Evidence from epidemiological studies has consistently demonstrated that long-term exposure to ambient air pollutants is associated with increased cardiovascular morbidity and mortality. The American Cancer Society (ACS) cohort study reported that people living in more polluted areas with high levels of particulate matter (PM) with aerodynamic diameter <2.5 μm ($PM_{2.5}$) were more likely to die from cardiopulmonary diseases and lung cancer than those in less polluted areas. An association between yearly average of PM with aerodynamic diameter <10 μm ($PM_{10}$) and increased risk for hospitalization for congestive heart failure or subsequent myocardial infarction has also been reported. To investigate the possible mechanisms linking long-term air pollution exposure with cardiovascular diseases, this study further reported associations of $PM_{2.5}$ with mortality from specific cardiopulmonary diseases and hypothesized that the general pathophysiological pathways of PM effects may include pulmonary and systemic inflammation, acceleration of atherosclerosis and alteration of cardiac autonomic function. Nevertheless, evidence linking long-term air pollution exposure to major cardiovascular risks/biomarkers in humans is still limited.

A recent epidemiological study of 2978 adults from the Third National Health and Nutrition Examination Survey (NHANESIII) demonstrated a link between long-term $PM_{10}$ exposure and white blood cell count (WBC), a non-specific haematological marker of inflammation. However, another study reported that there was no association between inflammatory markers of fibrinogen or C-reactive protein (CRP) and long-term exposure to outdoor air pollution, including $PM_{10}$, nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$) and ozone ($O_3$). A further study investigating the relationship between $PM_{2.5}$ and CRP showed a slightly increased risk, but it was not significant. Therefore, further evidence is needed to explore the effects of long-term air pollution exposure on more specific biomarkers in humans to confirm previous epidemiological studies. To address these scientific gaps, researchers in Taiwan conducted secondary data analyses to investigate the changes in blood pressure, blood lipids, blood sugar and inflammation markers in elderly subjects associated with changes in exposure to long-term ambient air pollution.

Secondary analyses were carried out of data on blood pressure and blood biochemistry markers from the Social Environment and Biomarkers of Aging Study in Taiwan and air pollution data from the Taiwan Environmental Protection Administration in 2000. Associations of 1-year averaged criteria air pollutants $PM_{10}$ and $PM_{2.5}$, $O_3$, $NO_2$, $SO_2$ and carbon monoxide (CO) with systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting glucose, haemoglobin A1c (HbA1c), interleukin 6 (IL-6) and neutrophils were explored by applying generalized additive models.

After controlling for potential confounders, it was observed that increased 1-year averaged particulate air pollutants ($PM_{10}$ and $PM_{2.5}$) and $NO_2$ were associated with elevated blood pressure, total cholesterol, fasting glucose, HbA1c, IL-6 and neutrophils. Associations of increased 1-year averaged $O_3$ with elevated blood pressure, total cholesterol, fasting glucose, HbA1c and neutrophils were also observed. In particular, two-pollutant models showed that $PM_{2.5}$ was more significantly associated with end-point variables than two gaseous pollutants, $O_3$ and $NO_2$.

Changes in blood pressure, blood lipids, blood sugar and haematological markers of inflammation are associated with long-term exposure to ambient air pollutants. This might provide a link between air pollution and atherosclerotic cardiovascular diseases.

***Source:*** Occupational and Environmental Medicine, Vol. 68, No. 1, Pages 64-68, January 2011.

# AIR POLLUTANTS AND THE DEVELOPMENT OF CARDIOVASCULAR DISORDERS

Cardiovascular disorders are becoming a frequent event in modern societies owing to contemporary life styles in the developed world. The degree of environmental contamination with toxins and particularly airborne pollution imposes stress on the heart which promotes the incidence of damaging cardiovascular events like arrhythmogenesis, myocardial infarction and cardiac hypertrophy. Air pollution is one such factor that promotes cardiac stress which leads to cardiovascular damage. Various epidemiological and clinical studies have highlighted the deleterious effects of air pollution on heart disease.

Air pollutants mainly include carbon monoxide, oxides of nitrogen, sulfur dioxide, ozone and particles composed of elemental carbon, organic carbon compounds, transition metals, metal oxides, acid concentrates, sulfates and nitrates. Of these, particulate matter has become a major concern of cardiovascular research. There is substantial evidence that indicates the effect of ambient particulate matter on cardiovascular health.

Airborne particulate matter is a heterogeneous mixture of solid and liquid particles of varying size and chemical composition. In 1987, the regulatory focus was on particles that could readily penetrate and deposit in the tracheobronchial tree, or $PM_{10}$ (PM with a median aerodynamic diameter of <10 μm). In 1997, the US EPA promulgated 24-h and annual average standards for $PM_{2.5}$ (PM with median aerodynamic diameter of <2.5 μm), comprising the size fraction that can reach the small airways and alveoli. The existing federal $PM_{10}$ standards were retained, however, to address health effects that could be related to the "coarse fraction" ($PM_{10-2.5}$; WHO Air Quality Guidelines, 1987, 2000). Particles of

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# CHRONIC LEAD EXPOSURE – A RISK FACTOR OF ARTERIAL HYPERTENSION DEVELOPMENT

The relationship between exposure to lead and arterial hypertension has been studied for over 80 years. Currently, an effect of lead on arterial blood pressure is accepted to depend on the dose and duration of the exposure. A single intoxication with a low dose of lead results in a transient hypertensive effect. High concentrations of lead, linked with symptoms of acute intoxication, decrease arterial blood pressure. Low doses of lead, which do not exceed maximum admissible concentrations but administered for a long time, cause permanent increase of arterial blood pressure in experimental animals. Numerous studies in recent years have yielded evidence indicating that chronic exposure of persons working chronically in conditions exposing them to lead compounds represents a risk factor of developing arterial hypertension.

Ambulatory blood pressure monitoring (ABPM) represents the most prognostically reliable method of measuring arterial blood pressure. Moreover, as compared to office blood pressure measurements, ABPM demonstrates a higher predictive value, as related to developing organ complications of arterial hypertension.

The accessible literature of the subject concentrates on the relationship between arterial hypertension, organ complications, and value of pulse pressure and also variability of arterial blood pressure. However, until now, no relationship between occupational exposure to lead and variability of arterial blood pressure and incidence of organ complications in persons with arterial hypertension has been documented.

Now, a new study aims at evaluating the relationship between occupational exposure to lead and manifestation of cardiovascular complications in patients with arterial hypertension. In this study an attempt was made to determine a relationship between organ complications and pulse pressure and variability of arterial blood pressure in persons with arterial hypertension chronically exposed to lead.

The study included 73 men (mean age, 54.26 years) with arterial hypertension, treated with hypotensive drugs: group I-persons occupationally exposed to lead and group II-individuals not exposed to lead. An analysis of results obtained during ABPM disclosed significantly higher values of mean systolic blood pressure, mean blood pressure, pulse pressure, and variability of systolic blood pressure in the group of hypertensive patients occupationally exposed to lead as compared to patients with arterial hypertension but not exposed to lead. The logistic regression showed that a more advanced age, higher concentration of blood zinc protoporphyrin, and a higher mean value of pulse pressure represented independent risk factors of left ventricular hypertrophy in the group of persons with arterial hypertension and chronically exposed to lead.

There are some limitations in this study. The main limitation is the relatively small number of the study group. However, both the lead-exposed and unexposed groups included more than 30 subjects and were fairly comparable and statistically significant results were obtained in the study. Moreover, differences in the incidence and severity of arterial hypertension complications observed between a group exposed to lead and not exposed could be explained by the different grade or severity of arterial hypertension. The statistically significant differences between the study groups that were found in the aspect of 24-hour ABPM seem to support that idea. The authors of the study have made attempts to make the studied groups comparable in severity of arterial hypertension. Selection criteria for the not exposed group were based on a case-to-case analysis. Not-exposed persons were matched to subjects exposed to lead compounds based on the criteria such as the same arterial hypertension grade according to European Society of Hypertension (ESH)/ European Society of Cardiology (ESC) guidelines and similar duration of arterial hypertension. Persons with secondary arterial hypertension were excluded from the study. Both studied groups did not differ in characteristics of the arterial hypertension treatment, also values of domestic blood pressure measurements with a mercury sphygmomanometer did not significantly differ. The significant differences in blood pressure between the studied groups were observed only when the sensitive diagnostic method was used, that is, 24-hour ABPM. Moreover, regression analysis showed the relationship between exposition to lead and manifestation of arterial hypertension complications. The obtained models demonstrated that higher blood lead level represented an independent risk factor of increased pulse pressure and that higher concentration of blood zinc protoporphyrin represented an independent risk factor of left ventricular hypertrophy in the group of persons with arterial hypertension chronically exposed to lead.

This work demonstrating that occupational exposure to lead represents an independent risk factor of increased pulse pressure in the group with arterial hypertension may be of key importance in the process of shaping general social awareness as to the harmful effects of lead compounds on human health. In persons with arterial hypertension occupationally exposed to lead, cardiovascular complications seem to be more clearly expressed and to be manifested with higher incidence than in persons with arterial hypertension not exposed to lead.

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***Source:*** Toxicology and Applied Pharmacology, Vol. 249, Issue 1, Pages 41-46, November 2010.

## AIR POLLUTANTS AND THE DEVELOPMENT OF CARDIOVASCULAR DISORDERS

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diameter less than $PM_{10}$ are considered to have deleterious effects on health. However, ultrafine particles (UFP), which have diameter less than $PM_{0.1}$ are an interesting area of research owing to their capability to penetrate deep into the lungs and may even to pass directly into the circulatory system. Such particles can thus have harmful effects on cardiovascular health. The present review focuses upon the various mechanisms that will explain how air pollutants, especially ambient particulate matter is affecting cardiovascular health and will throw light on various cardiovascular events which have been found to be influenced due to air pollution.

Although various studies indicate that ambient particulate matter in air pollution is most strongly allied to increased morbidity and mortality due to their link with cardiovascular adverse events, the mechanisms leading to these harmful effects on the cardiovascular system have not been defined clearly. However, several hypotheses have been proposed that elucidate the direct and indirect effects of air pollution. Adverse cardiovascular events such as thrombosis, vascular dysfunction, atherosclerosis, myocardial infarction an disturbance in cardiac autonomic control are thought to be linked with air pollution. Recently, an association has also been found between cardiac hypertrophy and air pollution. The present review focuses on highlighting the implications of air pollution in deteriorating cardiac health.

The review provides some perspective on the extent of the involvement of air pollutants (especially particulate matter) in various cardiovascular events. The exact mechanisms involved are unknown for the majority of events but these processes can be explored in terms of two major categories, i.e. direct translocation or via indirect secondary mediators. Inflammation prove is the most common mediator of the adverse cardiovascular events of air pollution like thrombosis, vascular dysfunction, etc. C-Reactive Protein, IL-6 and other inflammatory cytokines, fibrinogen and RhoA/Rho-Kinase are some of the key players involved in the processes. Such an analysis suggests that this area has a huge potential for future research in elucidating the exact mechanism pertaining to specific cardiovascular events. It is also important to understand the nature and pathways whereby lung tissue is damaged by air pollutants as well as cardiac events. These observations emphasize the need to control air pollution and devise strategies which will improve air quality, so reducing not only the risks of cardiovascular problems but also mortality and morbidity.

***Source:*** Environmental Toxicology and Pharmacology, Vol. 31, Issue 1, Pages 1-9, January 2011.

## Evaluation of Neurotoxic and Immunotoxic Effects of Trichloroacetic Acid on Rats

Environmental pollution by pesticide residues is a major environmental concern due to their extensive use in agriculture and in public health programs. Since pesticides are used for plant protection, there has been improvement in the control of pest population and spread of infection-borne disease vectors. Public health programs in many developing countries including Turkey where the present research study was conducted also utilize these studies as pesticides of choice to control disease-transmitting organisms. There is abundant evidence that many pesticides produce their acute toxic action by activating or inhibiting enzymes. In addition, chemicals via food chain have harmed physiological mechanisms in man. On the other hand, many chemicals at even relatively low dosages disturb the metabolism of biota by altering normal enzyme activity. A considerable literature exists describing the effects of pesticides on populations and communities of organisms under field conditions. Major effects of pesticides on animal and insect populations result primarily in significant changes in species abundance and associated shifts in dynamics; thus they have resulted in an imbalance in the natural system. The effects of trichloroacetic acid (TCA) in various vertebrates have already been investigated in several studies, but results concerning vertebrates are both very limited.

Moreover, there is still a considerable lack of information concerning TCA effects on neurotoxicity and immunotoxicity of vertebrates. Therefore a recent study was carried out to investigate the effects of TCA on rats at subchronic exposure.

The neurotoxic effects of TCA were evaluated by measuring the activities of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Biomarkers selected for immunotoxic monitoring were the activities of adenosine deaminase (ADA) and myeloperoxidase (MPO) in various tissues of rats exposed to 2000 parts per million (ppm) dosage of TCA for 52 days. Results showed that the administration of TCA decreased BChE activities in heart and lung tissue of rats treated with TCA. With regard to the immunotoxic effects, ADA activity significantly decreased in the heart, lungs and spleen whereas MPO activity increased after subchronic exposure with 2000 ppm dosage in all of the tissues except for heart tissue of rats compared with controls. These observations led researchers to conclude that the administration of TCA at subchronic doses decreased BChE and ADA activities but increased MPO activity in various tissues of rats. This may reflect the potential role of these parameters as useful biomarkers for toxicity of TCA.

***Source:*** Toxicology and Industrial Health, Vol. 26, No. 10, Pages 725-731, November 2010.

# EFFECTS OF LOW-LEVEL LEAD EXPOSURE ON RETINAL CELL PRODUCTION IN MICE

Perinatal exposure to environmental toxicants such as lead, methylmercury, pesticides, and polychlorinated biphenyls increases the risk of developmental disabilities, mental retardation, neurosensory alterations, and psychiatric morbidity. The spectrum of neurotoxic effects depends on the perinatal period of exposure, concentration and duration of exposure, and genetic susceptibility. This is best exemplified by lead exposure, which is especially neurotoxic to the developing central nervous system: Children with blood lead concentrations (BPb) <10 µg/dL – the current low level of concern – have cognitive deficits and neurosensory alterations.

The phenotype of retinal alterations is markedly dependent on the developmental exposure period. After postnatal lead exposure, rod photoreceptor-selective apoptosis, persistent rod-mediated (scotopic) electroretinographic (ERG) subnormality, and scotopic behavioral deficits occur in humans, monkeys, and rodents. In contrast, children, monkeys, and rats with low-dose (≤10 µg/dL) to moderate-dose (~25 µg/dL) gestational lead exposure (GLE) exhibit novel scotopic ERG supernormality.

The adult mammalian retina consists of six neuronal cell types and a Müller glial cell (MGC) that originate from a pool of multipotent retinal progenitor cells (RPCs). Retinogenesis proceeds in two distinct yet overlapping histogenetic periods, characterized by the development of early-born cells (ganglion, horizontal, cone, and amacrine cells) mostly during embryogenesis and late-born cells [rods, bipolar cells (BCs), and MGCs] during early postnatal development. Approximately 70% of adult [postnatal day 60 (PND60)] mouse retinal cells are rods, and 20% are BCs. Extrinsic factors such as neurotransmitters and modulators alter the cell fate of RPCs; however, these changes are limited by the intrinsic properties of RPCs. Low-dose and moderate-dose GLE produced a novel retinal phenotype in PND60-PND90 rats characterized by an increased number of cells in the outer nuclear layer and inner nuclear layer with no change in glial fibrillary acid protein content, suggesting that GLE selectively increased the number of late-born neurons but not MGCs.

The goals of the present study were to use the mouse model of GLE to test the hypothesis that GLE selectively increases neurons in the scotopic signaling pathway and to determine the cellular mechanisms underlying the phenotype. To accomplish this, researchers determined the number and distribution of early- and late-born retinal cell types in PND60 control and GLE offspring; kinetics of RPC mitosis, proliferation, and cell-specific apoptosis during development; and spatiotemporal pattern and number of developing late-born cells with 5-bromo-2-deoxyuridine birth dating. The results reveal that GLE increases and prolongs RPC proliferation without decreasing apoptosis. This produced an adult retina with normal lamination and a selectively increased number of rods and BCs.

The findings of this study stress the importance of examining developmental-stage-dependent and dose-dependent effect in human and animal toxicology studies.

The non monotonic effects suggest that high-dose (~40 µg/dL) GLE also triggered rod apoptosis similar to that observed in mice and rats with postnatal-only lead exposure.

As suggested by other retinal studies, the increased number of rods in GLE mice may accelerate age-related retinal degeneration.

The findings of the present study raise complex issues for neurotoxicologists, pediatricians, public health regulators, and risk assessors.

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***Source:*** Environmental Health Perspectives, Vol. 119, No. 1, Pages 71-77, January 2011.

# *Bisphenol A on Dollar Bills and Receipts – Potential Toxic Effects*

A hormone-disrupting chemical, linked to serious health problems such as cancer, infertility, and early puberty has now invaded our lives through everyday exposure. The chemical is bisphenol A (BPA) and its presence is found in dollar bills and receipts, as well as in food and drink containers.

The Safer Chemicals, Healthy Families Coalition and Washington Toxics Coalition set out to track down the trail of BPA in the US population by testing cash register receipts and paper money.

Receipts and dollar bills were collected from a total of 20 states and Washington, D.C. and tested for BPA. It was found that approximately 50% of thermal paper receipts are made with large quantities of unbound BPA which transfers easily from thermal paper to human skin.

Several chemicals can function as the developer in thermal paper, but many manufacturers choose BPA, a chemical most associated with the clear, hard plastic typical of baby bottles and sports bottles. But BPA is a chemical of many uses, which include those bottles but also medical devices, optical media like CDs, epoxy linings in food cans, and flame retardants.

Most Americans became aware of the dangers of BPA in the context of it leaching from baby bottles and potentially harming the youngest children. Parents were shocked that such a basic tool of parenting was delivering a toxic chemical to babies. And manufacturers responded to their outrage. Once the problem was widely recognized, all of the major baby bottle companies moved quickly to replace BPA-containing polycarbonate bottles with alternatives, and major retailers removed bottles and sippy cups with BPA from their shelves. Seven states and a number of other governments have now acted to make sure all baby bottles sold within their borders are free of BPA.

But while attention was focused on addressing the problem of BPA

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# EFFECTS OF SILVER NANOPARTICLES ON NEURODEVELOPMENT IN PC12 CELLS

The rapid growth in the commercial use of silver nanoparticles (AgNPs) is increasing silver exposure in the general population. AgNPs are incorporated into products primarily as an antimicrobial, reflecting their release of monovalent silver ion ($Ag^+$). However, the same mechanisms that make $Ag^+$ an antimicrobial also render it a potential developmental neurotoxicant. Silver crosses the placenta and concentrates in the human fetus, achieving higher concentrations than in the mother. Animal studies show accumulation in the developing brain, developmental dysmorphology, and behavioral changes in exposed adults. Importantly, AgNP exposure via either inhalation or oral routes also leads to Ag accumulation in the adult rodent brain, altering the expression of genes involved in neuronal function.

Researchers recently showed that in PC12 cells, a well-established model of neuronal development, $Ag^+$ disrupts key mechanisms involved in cell replication and neurodifferentiation; they then demonstrated that nervous system development is disrupted in developing zebrafish exposed to $Ag^+$. Unlike primary neuronal cultures, PC12 cells provide a homogeneous population that continues to divide until differentiation is triggered by addition of nerve growth factor. Accordingly, this model allows direct study of effects on DNA synthesis associated with cell replication, an important target of neurotoxicants; the cells then differentiate into distinct acetylcholine and dopamine phenotypes.

It is thus critical to assess the extent to which AgNPs can elicit the same or different types of neurodevelopmental outcomes as $Ag^+$. In the same PC12 model, high concentrations of AgNPs disrupt the cell membrane and impair mitochondrial function while altering gene expression related to oxidative stress; however, these studies were not carried out in the context of neurodifferentiation.

Now a new study has compared the effects of AgNPs with $Ag^+$ in PC12 cells for neurodevelopmental end points including cell replication, oxidative stress, cell viability, and differentiation.

First, researchers compared citrate-coated AgNPs (AgNP-Cs) with $Ag^+$, and then assessed the roles of particle size, coating, and composition by comparing AgNP-C with two different sizes of polyvinylpyrrolidone-coated AgNPs (AgNP-PVPs) or silica nanoparticles.

In undifferentiated cells, AgNP-C impaired DNA synthesis, but to a lesser extent than an equivalent nominal concentration of $Ag^+$, whereas AgNP-C and $Ag^+$ were equally effective against protein synthesis; there was little or no oxidative stress or loss of viability due to AgNP-C. In contrast, in differentiating cells, AgNP-C evoked robust oxidative stress and impaired differentiation into the acetylcholine phenotype. Although the effects of AgNP-PVP showed similarities to those of AgNP-C, the researchers also found significant differences in potencies and differentiation outcomes that depended both on particle size and coating. None of the effects reflected simple physical attributes of nanoparticles, separate from composition or coating, as equivalent concentrations of silica nanoparticles had no detectable effects.

AgNP exposure impairs neurodevelopment in PC12 cells. Further, AgNP effects are distinct from those of $Ag^+$ alone and depend on size and coating, indicating that AgNP effects are not due simply to the release of $Ag^+$ into the surrounding environment.

***Source:*** Environmental Health Perspectives, Vol. 119, No. 1, Pages 37-44, January 2011.

## *Bisphenol A on Dollar Bills and Receipts – Potential Toxic Effects*

*(Continued from page 7)*

leaching from plastic, companies were using it on an item people handle every day, cash register receipts. And unlike its use in baby bottles, the BPA on receipt paper isn't chemically bound in any way: it is free BPA and as results show, it moves easily from paper to people. Apparently, it also moves from receipts to other items in everyday use, like money.

The recent study commissioned by Safer Chemicals, Healthy Families and Washington Toxics Coalition stressed the seriousness of the current situation and the urgent need to reduce or eliminate the use of known toxics that can cause cancer, disrupt hormones, cause reproductive harm and infertility, or cause learning disabilities, to which the population is currently exposed in products in daily use.

***Source:*** Safer Chemicals, Healthy Families and Washington Toxics Coalition, December 2010 – http://blog.saferchemicals.org/2010/12/on-the-money-bpa-in-dollar-bills-and-receipts.html.


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