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# *Health Effects of Exposure to Environmental Carbon Monoxide: Negative Effects on Cardiac Autonomic Function in People with Metabolic Syndrome*

Despite improvements in air quality, air pollution is still a major environmental health issue. Substantial epidemiological studies have consistently demonstrated adverse effects of air pollution, even that within air quality standards, on cardiovascular health.

Carbon monoxide (CO) is a colorless, odorless, tasteless, and toxic gas produced primarily during the incomplete combustion of carbonaceous fuels and substances.

The association between CO exposure and adverse cardiovascular outcomes has been well supported by previous findings. Recent studies have implicated greater susceptibility in groups exhibiting a pre-existing increased risk for heart disease, including older subjects and patients with heart disease. Based on these findings, it is conceivable that individuals with a pre-existing increased risk for heart disease, but no diagnosed cardiovascular disease, may also be more susceptible to the effects of CO exposure on heart function. One group of such individuals consists of those with metabolic syndrome (MetS), a combination of risk factors for cardiovascular disease and diabetes that has recently received increased attention due to increase in both prevalence and recognition. In a new study, researchers investigated the effects of CO exposure on cardiac autonomic function by measuring the heart rate variability (HRV), a widely used method for assessing cardiac autonomic balance. Specifically, it was hypothesized that subjects with MetS, a group at high risk for cardiovascular disease, would be more vulnerable to the adverse effects of CO. Thus, the study compared cardiac autonomic changes with CO exposure in subjects with and without MetS.

It also explored the relationship between CO exposure and specific components of MetS. Data were obtained from air pollution measurements and from health examinations on a total of 986 subjects, from a Korean community. Measurements of the 5-min HRV and examinations for MetS were conducted, and a linear regression model with a time lag was evaluated for any association. The group with MetS showed a significant reduction in the standard deviation of the normal-to-normal intervals and in the high frequency domain of HRV. After adjusting for age, sex, smoking status, day of the week effect, month effect, temperature, and relative humidity, these declines were significantly associated with exposure to CO for 25 to 48 h prior to the HRV measurement. Evidence for effect-modification by two specific MetS components, fasting blood glucose and triglycerides, was also observed in relation to CO exposure. These results suggest that CO exposure may trigger changes in cardiac autonomic function, and that subjects at high risk for heart disease may be more susceptible to CO effects.

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***Source:*** Science of the Total Environment, Vol. 407, Issue 17, August 2009.

# GENOTOXIC EFFECTS OF SOLVENTS USED IN SHOE MANUFACTURING

Cytogenetic risk associated with occupational exposure to organic solvents is still subject to debate.

A recent study carried out in the city of Leon, Mexico where shoe manufacturing is the main industrial activity, sets out to identify and quantify primary solvents present in the air environments of shoe factories in search of a possible relationship between the exposure conditions and the micronuclei frequency in the cells of buccal mucosa as a marker of genotoxic damage.

Thirty-four exposed shoe workers and 34 unexposed control subjects, paired by age and sex, were compared. Occupational exposure was determined by using 3M monitors. Solvents were assessed by gas chromatography. Exfoliated buccal cells were obtained from each subject to determine the incidence of micronuclei and other nuclear abnormalities. One thousand cells were counted in each subject. Solvents detected were acetone, ethyl acetate, methyl ethyl ketone, and toluene. The incidence of nuclear abnormalities was significatively higher in the exposed group when compared to the control group. A positive relationship between the incidence of micronuclei and the toluene concentration in the environment was found.

The full list of organic solvents screened in this study included: acetone, methyl ethyl ketone, ethyl acetate, benzene, methyl isobutyl ketone, toluene, butyl acetate, *m*-xylene, *o*-xylene and *p*-xylene. The results obtained by gas chromatography with flame ionization detector (GC-FID) allowed for the identification of formaldehyde, acetaldehyde, methyl ethyl ketone and acetone, all of them at lower levels as compared to Mexican Official Norm regulations. On the other hand, the primary solvent detected at relatively high levels (range 6.3-362.9 mg/m$^3$) was toluene, indicating contamination of some work sites with this compound (threshold limit value-time-weighted average – TLV-TWA 188 mg/m$^3$). To gain a further insight on the genotoxic potential of the identified aldehydes and solvents, the frequency of micronuclei and other nuclear anomalies was assessed in the exfoliated cells of the buccal mucosa in exposed workers and in control subjects.

In the present study, the researchers believe that the novelty of their contribution relies on the detection and quantification of all solvents present in the breathing zone of individual workers and relating the results obtained to cytogenetic damage as measured by micronuclei test. Among several solvents typically associated with shoe making, toluene, acetone, methyl ethyl ketone and ethyl acetate were found, yet only the concentrations of toluene were higher than those indicated by Mexican Official Norm. It should be stressed that the concentrations of all solvents were taken for multiple regression analysis. The results obtained showed a statistically important positive correlation between the frequency of micronuclei and the toluene exposure, but no relation was found for other solvents. The results obtained in this work suggest that the cytogenetic damage is a global, cumulative effect of all actual risk factors. In the subjects of this study, the important risk factors were exposure to toluene, smoking habit and alcohol consumption.

Further studies in relation to possible synergistic effects of tobacco, alcohol and organic solvents are required. The use of the micronuclei test in exfoliated cells of the buccal mucosa is suggested to monitor the effect of genotoxic agents in the population at risk. This is an easy, effective and low-cost test.

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***Source:*** International Archives of Occupational and Environmental Health, Vol. 82, No. 3, February 2009.

# Potential Relationship between Early-life Toxicant Exposure and Subsequent Diet-related Disease

It has been suggested that widespread exposure to a variety of neurotoxic chemicals is a potential factor behind what has been called a "silent pandemic" of autism spectrum disorders, learning disabilities, and other neurodevelopmental disorders. Exposure to organophosphate insecticides is of particular concern because these widely used compounds have been shown in rodents to induce persistent synaptic abnormalities in neural acetylcholine (ACh) systems at doses too low to cause symptoms of systemic exposure. Pilot studies have reported some evidence of improvement when a "ketogenic" diet—high in fat and low in carbohydrates—was used to treat certain neurologic disorders. Drawing from this preliminary clinical research, researchers have now demonstrated that many of the abnormalities in ACh systems produced by neonatal organophosphate exposure were not evident in adult rats fed a high-fat diet.

Rats were injected with the organophosphate parathion on each of postnatal days 1-4, at doses of 0.1 or 0.2 mg/kg/day-these dosages straddle the threshold at which cholinesterase inhibition is first detectable. In adulthood, half the animals were switched to a high-fat diet for 8 weeks. The investigators then examined brain regions of the rats to assess specific aspects of ACh synaptic function, including nicotinic ACh receptor binding, choline acetyltransferase activity, and hemicholinium-3 binding to the presynaptic choline transporter.

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## Potential Relationship between Early-life Toxicant Exposure and Subsequent Diet-related Disease

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Adult rats on a standard lab chow diet showed multiple abnormalities in regional ACh synaptic markers following parathion exposure. All seven abnormalities observed in parathion-exposed females on the standard diet were absent in exposed females on the high-fat diet, and eight of ten abnormalities observed in parathion-exposed males on the standard diet were absent in exposed males on the high-fat diet.

The results clearly indicate that consuming a high-fat diet in adulthood can ameliorate many of the long-term ACh synaptic abnormalities evoked by neonatal parathion exposure. These findings provide a proof of principle that dietary interventions are capable of offsetting the ACh synaptic defects caused by developmental neurotoxicant exposure.

Moreover, the results of the present study point to an important consideration in the explosive worldwide increase in obesity. It is clear that neurodevelopmental disorders can influence apparent lifestyle choices, most notably in the increased incidence of drug abuse or cigarette smoking. A recent study showed that abstinence from smoking in adolescent smokers whose mothers smoked during pregnancy leads to cognitive impairment, whereas those who were born to nonsmokers showed cognitive improvement upon abstinence from smoking. In other words, where there was preexisting neurodevelopmental damage from prenatal tobacco exposure, adolescents were able to offset cognitive impairment by smoking; this likely contributes to the higher likelihood of the children born to smoking women becoming smokers themselves. By the same token, the present studies point to the possibility that exposure to developmental neurotoxicants could contribute to a subsequent preference for a high-fat diet as a way of ameliorating the effects, thus providing an indirect but potentially potent driving force for consuming an unhealthy diet. If this turns out to be true, then the findings point to a potentially important contributory factor in the increased incidence of obesity and diabetes, expanding the public health implications of the "silent pandemic" caused by developmental neurotoxicant exposure.

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***Source:*** Environmental Health Perspectives, Vol. 117, No. 6, June 2009.

## Lead Intoxication from the Recycling of Used Lead-acid Batteries

Lead is a toxic metal whose widespread use has caused extensive environmental contamination and health problems in many parts of the world. Lead exposure accounts for almost 1% of the global burden of disease, with the highest burden in developing regions. Measures to reduce and control lead use and prevent human exposure to lead, in particular for children, have been put in place at national and international levels. However, serious lead intoxications still occur from different sources, in particular in developing countries, posing a major health and environmental challenge.

Between November 2007 and March 2008, a cluster of 18 deaths caused by a severe and rapidly progressive central nervous system disease of unexplained origin was identified in young children living in the NGagne Diaw neighborhood of Thiaroye sur Mer, in the suburbs of Dakar, Senegal. Local health authorities conducted initial investigations to identify the cause of the outbreak. Differential diagnoses included cholera, meningitis, and cerebral malaria, as these conditions are prevalent at that time of the year; however, investigations disproved these diagnoses. Lead intoxication was then considered because the mothers of some of the children were engaged in the recycling of used lead-acid batteries (ULAB) and the recovery of lead particles from contaminated sand taken from the battery breaking areas. Initial investigations conducted by the Dakar Poisons Centre detected very high blood lead levels in 71 siblings and mothers of the deceased children. Concerned about these findings, the Senegalese Ministry of Health requested the assistance of the World Health Organization (WHO) in investigating and responding to this incident.

Because autopsies were not possible, the investigation centered on clinical and laboratory assessments performed on 32 siblings of deceased children and 23 mothers and on 18 children and 8 adults living in the same area, complemented by environmental health investigations.

All 81 individuals investigated were poisoned with lead, some of them severely. The blood lead level of the 50 children tested ranged from 39.8 to 613.9 µg/dL with a mean of 129.5 µg/dL. Seventeen children showed severe neurologic features of toxicity. Homes and soil in surrounding areas were heavily contaminated with lead (indoors, up to 14,000 mg/kg; outdoors, up to 302,000 mg/kg) as a result of informal ULAB recycling.

The investigations revealed a mass lead intoxication that occurred through inhalation and ingestion of soil and dust heavily contaminated with lead as a result of informal and unsafe ULAB recycling. Circumstantial evidence suggested that most or all of the 18 deaths were due to encephalopathy resulting from severe lead intoxication. Findings also suggest that most habitants of the contaminated area, estimated at 950, are also likely to be poisoned. This highlights the severe health risks posed by informal ULAB recycling, in particular in developing countries, and emphasizes the need to strengthen national and international efforts to address this global public health problem.

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***Source:*** Environmental Health Perspectives, Vol. 117, No. 10, October 2009.

# BONE LEAD AND ENDOGENOUS EXPOSURE IN AN ENVIRONMENTALLY EXPOSED ELDERLY POPULATION

Environmental exposure to lead in the United States has been reduced substantially over the last several decades. However, lead stores in bone because of past lead exposure remains a problem for the general public. Unlike lead in blood, with a half-life of approximately 30 days, lead in bone has a half-life of many years to decades. More than 95% of lead in the human body resides in bone. Hence, bone is a major deposition site for lead and bone lead is an indicator of cumulative exposure. The use of lead in gasoline, soldering, and paint is mostly responsible for the lead stored in bones in the general population. Although these sources have been greatly reduced, they continue to contribute as a significant source of lead exposure for the general population through endogenous exposure. That is, lead stored in bone serves as an endogenous source of exposure because it is gradually released to blood through bone resorption. In a recent project, researchers investigated the endogenous exposure in an environmentally exposed elderly population. Environmentally exposed elderly men had moderate to high lead exposure history in the past, which could create significant bone lead stores. Elderly men also go through increasing bone loss, which could contribute to higher endogenous exposure. In addition, lead exposure leads to increased blood pressure levels and decline of cognitive function, which are more prevalent in the elderly population. All these facts render endogenous exposure to lead in environmentally exposed elderly men a significant public health issue.

The present study examines the association between bone lead and current blood lead in a large environmentally exposed elderly male population, and how it may vary due to age and bone resorption rates. Bone lead is assessed with *in vivo* K-x-ray fluorescence. Urine cross-linked N-telopeptides of type I collagen (NTx), derived from bone collagen degradation, is considered a sensitive and specific marker of bone resorption.

Researchers tested the association between current blood lead and bone lead in an environmentally exposed population, which has been shown to be significant in previous studies. This study is unique in that the sample population is relatively large and hence allows the exploration and testing of the effect of age, levels of exposure, and bone resorption on the bone-blood association. This is the first study that explores the nonlinearity of the association between bone lead and blood lead and the effect of age and bone resorption on the association in the same population for environmentally exposed people.

For the current study, 776 participants who had their tibia and patella bone lead, as well as blood lead measured at least once were identified; 427 of them had both their tibia lead and patella lead measured twice, 197 three times, and 47 four times, for a total of 1447 observations. Among the 776 participants and 1447 observations, 746 participants and 1377 observations had a complete data including all covariates. Of these 776 subjects, 642 had at least one NTx measurement, and all lead measurements (tibia, patella, and blood lead), and 610 had a complete data. The average values of tibia lead, patella lead, and blood lead, were not significantly different between the subjects with and without complete data. Other subject characteristics (age, current smoking status, number of years of education, and daily alcohol intake) did not differ either.

One of the limitations of the study is that the model adjusted only for current smoking status, alcohol intake, period, and number of years of education. Other potential factors that might affect current lead exposure, e.g., the working status of the subject, age of the household, whether there is lead paint in the house etc, are not adjusted. This may affect the association coefficients and the significance of the association between blood lead and bone lead.

The findings are consistent with the hypothesis that there is significant endogenous lead release from bone to blood in elderly men. The findings also indicate that the associations between both tibia and patella lead concentrations and blood lead are nonlinear.

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***Source:*** Journal of Occupational and Environmental Medicine, Vol. 51, No. 7, July 2009.

# Fine-Particulate Air Pollution and Life Expectancy in the United States

***Exposure to fine-particulate air pollution has been associated with increased morbidity and mortality, suggesting that sustained reductions in pollution exposure should result in improved life expectancy. A recent study has directly evaluated the changes in life expectancy associated with differential changes in fine-particulate air pollution that occurred in the United States during the 1980s and 1990s.***

Researchers compiled data on life expectancy, socioeconomic status, and demographic characteristics for 211 county units in the 51 U.S. metropolitan areas with matching data on fine-particulate air pollution for the late 1970s and early 1980s and the late 1990s and early 2000s. Regression models were used to estimate the association between reductions in pollution and changes in life expectancy, with adjustment for changes in socioeconomic and demographic variables and in proxy indicators for the prevalence of cigarette smoking.

Improvements in life expectancy during the 1980s and 1990s were associated with reductions in fine-particulate pollution across the study areas, even after the above mentioned adjustment for various socioeconomic, demographic, and proxy variables for prevalence of smoking that are associated with health through a range of mechanisms. Indirect calculations point to an approximate loss of 0.7 to 1.6 years of life expectancy that can be attributed to long-term exposure to fine-particulate matter at a concentration of 10 $\mu g/m^3$, with the use of life tables from the Netherlands and the United States and risk estimates from the prospective cohort studies. In the present analysis, a decrease of 10 $\mu g/m^3$ in the fine-particulate concentration was associated with an estimated increase in life expectancy of approximately 0.61±0.20 year – an estimate that is nearly as large as these indirect estimates.

For the approximate period of 1980 through 2000, the average increase in life expectancy was 2.72 years for the counties in this analysis. Reduced air pollution was only one factor contributing to increased life expectancies, with its effects overlapping with those of other factors. On the basis of the average reduction in the $PM_{2.5}$ concentration (6.52 $\mu g/m^3$) in the metropolitan areas included in this analysis, the average increase in life expectancy attributable to the reduced levels of air pollution was approximately 0.4 year. Multicausality and competing risk issues make it difficult to quantify changes in life expectancy attributable to single risk factors, but these results suggest that the individual effect of reductions in air pollution on life expectancy was as much as 15% of the overall increase. In metropolitan areas where reductions in $PM_{2.5}$ were 13 to 14 $\mu g/m^3$, the contribution of improvements in air quality to increases in life expectancy may have been as much as 0.82 year.

In previous cross-sectional analyses, investigators have observed associations between mortality rates and particulate-air pollution, but the size of these associations was sensitive to efforts to control the analyses for potential confounders. The present analysis showed similar sensitivity for the strictly cross-sectional associations with life expectancy. The primary strength of this analysis, however, is the additional use of temporal variations. The availability of data on changes in pollution exposure across metropolitan areas from 1980 to 2000 provides the opportunity for an assessment that is similar to a natural experiment. Cross-sectional characteristics that do not change over time are controlled as if by design. Characteristics that affect life expectancy and that change over time – but not in correlation with changes in pollution – are unlikely to confound the results. Even with underlying spatial correlations, if the temporal changes in these characteristics are relatively less correlated, adjusted effect estimates from temporal regression models are likely to be more robust. In this analysis of differences in temporal changes, the estimated effects of reduced $PM_{2.5}$ exposure on increases in life expectancy were robust in analyses adjusted for socioeconomic, demographic, and proxy variables for the prevalence of smoking, as well as in an analysis restricted to large counties.

From an analytic perspective, it would have been informative if pollution had actually increased in some of the areas that were initially less polluted. However, pollution did not increase in any of the metropolitan areas, and the potential for reducing pollution was greater in the areas that were more polluted initially than in those that were less polluted. Stratified analyses showed no significant differences in pollution effects for the areas that initially had low or high pollution, which is consistent with previous findings on the effects of $PM_{2.5}$ even at relatively low concentrations.

In conclusion, the results of this analysis are generally good news. Although multiple factors affect life expectancy, the findings provide evidence that improvements in air quality have contributed to measurable improvements in human health and life expectancy in the United States.

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***Source:*** The New England Journal of Medicine, Vol. 360, No. 4, January 2009.

# EFFECTS OF CADMIUM EXPOSURE DURING PREGNANCY

***In adult humans, estimated exposures of 30-50 μg of $Cd^{2+}$ per day have been linked to increased risk of bone fracture, cancer, kidney dysfunction and hypertension. A wide spectrum of deleterious effects on the reproductive tissues and the developing embryo has also been described. $Cd^{2+}$ effects as an endocrine disruptor have been well documented; it has potent oestrogen and androgen-like activities in vitro and in vivo by targeting oestrogen and androgen receptors. In addition, $Cd^{2+}$ was shown to inhibit progesterone synthesis in placental tissues presumably through a dose-dependent decline in P450scc and 3β-HSD mRNAs.***

Previous studies have demonstrated that newborns delivered from mothers who smoked during pregnancy had reduced birth weight, compared to non-smokers, which was highly correlated with placental levels of $Cd^{2+}$. Additionally, placentas of mothers delivering low birth weight (LBW) neonates showed significantly higher $Cd^{2+}$ concentrations than placentas associated to normal birth weight neonates, suggesting that placental accumulation of heavy metals could be related to altered foetal growth mechanisms.

Altered foetal growth is associated with increased perinatal morbidity and impacts on health in later life, although abnormal foetal growth is actually not a constant or an imperative requirement of developmental programming of adult disease. Many studies in humans and animals have shown that LBW is associated with altered hypothalamus-pituitary-adrenal axis activity in later life; an embryo exposed to increased glucocorticoids (GC) concentrations shows LBW and later deleterious consequences in adult life. The adverse effects of GC exposure are partially related to changes in the expression of the glucocorticoid receptor (GR). 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), one of the most important regulators of GC in placental tissues, forms a functional barrier, restricting the free transfer of cortisol (human) or corticosterone (rat) between the maternal and foetal compartments by converting cortisol to cortisone (human) and corticosterone to 11-dehydrocorticosterone (rat).

It has been proposed that attenuation of placental 11β-HSD2 activity may lead to inappropriately high levels of corticosteroids which in turn results in intrauterine growth retardation and foetal programming of adult disease. However, contradictory results have been published about this point. It seems that the impact of GC exposure to foetal tissues depends on dose and type of GC, window of exposure, sex and stage of development of the foetus and animal model, suggesting that part of differences in the outcome may be related to the critical window of development of each organ, species and sex.

$Cd^{2+}$ has been reported to inhibit 11βHSD2 activity and expression in cultured trophoblast cells of human placenta. However, it is unknown whether $Cd^{2+}$ exposure during gestation induces alterations of placental GC metabolism and thus increasing foetal GC levels, a factor contributing to LBW.

Thus a new study has been conducted in which pregnant rats were first treated with different doses of $Cd^{2+}$ during pregnancy to find the lowest dose able to induce a significant decrease in the offspring's birth weight.

Researchers hypothesized that LBW induced by prenatal exposure to $Cd^{2+}$ is, at least in part, mediated by higher foetal exposure to GC, specifically corticosterone, the main active GC in rodents.

Pregnant rats were exposed to different dose of $CdCl_2$ administered in drinking water during the whole pregnancy period. At term, corticosterone was measured by enzyme immunoassay in maternal and foetal blood and in placental tissues. $Cd^{2+}$ was determined in placentas, maternal tissues (liver and kidney) and foetuses by inductively coupled plasma-mass spectrometry. Placental 11βHSD2 activity and expression were determined by a radiometric conversion assay and quantitative RT-PCR respectively. Results demonstrated that 50 ppm of $Cd^{2+}$, which was accumulated in different maternal tissues but not in the foetus, reduced pup birth weights and increased plasma corticosterone concentrations, both in mother and foetus. Placental 11βHSD2 activity and expression did not change by the treatment. The researchers concluded that 50 ppm of $Cd^{2+}$ administered during pregnancy increased foetal corticosterone concentrations due, probably, to alterations of the regulatory mechanisms of placental barrier to GC causing a mild but significant reduced birth weight.

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***Source:*** Toxicology Letters, Vol. 188, Issue 3, August 2009.

# EFFECTS OF PYRETHROIDS ON MOTOR ACTIVITY IN RATS

Pyrethroids are neurotoxic insecticides used in a variety of indoor and outdoor pesticide applications, including veterinary, agriculture and home pest control.

Pyrethroids have been classified as type I or type II based on acute high-dose biological effects and chemical structure. Type I compounds lack an $\alpha$-cyano group on the phenoxybenzyl moiety and produce toxic signs characterized by aggressive sparring and tremors (T syndrome). Type II compounds contain an $\alpha$-cyano group on the phenoxybenzyl moiety, and acute exposures produce a syndrome characterized by choreoathetosis and salivation (CS syndrome). A limited number of pyrethroids elicit both tremors and salivation and have been classified as type I/II or TS syndrome compounds.

In the United States, the Food Quality Protection Act (FQPA 1996) requires the U.S. Environmental Protection Agency to consider the cumulative risk of chemicals having a common "mechanism of toxicity." For chemicals considered to have a common mechanism of toxicity (commonality of target tissue, target site, and primary toxicologic effects for the members of a chemical class), dose additivity is the default hypothesis for assessing the hazard of mixtures. The overall assumption under dose additivity is that the toxicity of each component of the mixture behaves as a known dilution of a reference chemical selected as the index compound. This approach was used for the cumulative risk assessment of cholinesterase-inhibiting organophosphate and carbamate pesticides.

Previous research characterized the acute dose-effect functions for 11 pyrethroids administered orally in corn oil based on assessment of motor activity.

Now current research efforts aim at determining whether or not pyrethroid pesticides share a common mechanism and may thus be subject to cumulative risk assessment.

A new study, which is part of these efforts, uses a mixture of these 11 pyrethroids and the same testing paradigm used in single compound assays to test the hypothesis that cumulative neurotoxic effects of pyrethroid mixtures can be predicted using the default dose-addition theory.

Mixing ratios of the 11 pyrethroids in the tested mixture were based on the ED30 (effective dose that produces a 30% decrease in response) of the individual chemical (i.e., the mixture comprised equipotent amounts of each pyrethroid). The highest concentration of each individual chemical in the mixture was less than the threshold for inducing behavioral effects. Adult male rats received acute oral exposure to corn oil (control) or dilutions of the stock mixture solution. The mixture of 11 pyrethroids was administered either simultaneously (2 hr before testing) or after a sequence based on times of peak effect for the individual chemicals (4, 2, and 1 hr before testing). A threshold additivity model was fit to the single-chemical data to predict the theoretical dose-effect relationship for the mixture under the assumption of dose additivity.

When subthreshold doses of individual chemicals were combined in the mixtures, researchers found significant dose-related decreases in motor activity. Further, no departure was found from the predicted dose-additive curve regardless of the mixture dosing protocol used.

The present data demonstrate that subthreshold doses of individual pyrethroids, when combined in a mixture, produce measurable neurotoxicity in rats. These findings provide the first *in vivo* evidence of cumulative actions of pyrethroid mixtures in mammals and suggest that dose-additive approaches should be used for considering the combined toxicity of pyrethroid insecticides.

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***Source:*** Environmental Health Perspectives, Vol. 117, No. 10, October 2009.

# Occupational Pesticide Exposure and Inhibition of Cholinesterases

There is widespread use of agricultural pesticides in developing countries. Organophosphate pesticides (OPs) are triesters of phosphoric acid. OPs became widely used as the environmentally persistent organochlorine pesticides were banned in the 1970s. OPs gained popularity in the early 1980s because they were relatively inexpensive, readily available, less persistent in the environment, and less susceptible to pest resistance.

Exposures to OP pesticides occur generally, by three routes: (1) ingestion of residues in food and water, (2) dermal penetration of residues deposited on clothing and skin and dermal contact with contaminated surfaces, and (3) inhalation of airborne vapors and aerosol/particulate matter. On entering the body, OPs can be enzymatically converted to their oxon form and then react with available cholinesterase. Only OPs with a P=O moiety can interact with actylcholinesterase (AChE). Since most OP insecticides are organothiophosphates, they require metabolic activation to their corresponding oxygen analogs. Such activation is mediated by various isozymes of cytochrome P450, which are also involved in the detoxication of OPs. In addition, OPs can be

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## Occupational Pesticide Exposure and Inhibition of Cholinesterases

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detoxified hydrolytically by the action of A-esterase. One of the A-esterases is paraoxonase (PON1), which can hydrolyze the oxygen analogs of various commonly used OPs and some nerve agents.

The molecular target of OP-induced acute toxicity is AChE, whose inhibition in synapses and neuromuscular junctions causes the accumulation of the neurotransmitter acetylchloine, inducing overstimulation of the nervous system. In addition, OPs covalently bind to other serine esterases, primarily butyrylcholinesterase (BuChE), carboxyesterase (CaE), neuropathy target esterase (NTE), trypsin and chymotrypsin. Long-term effects possibly arise from continued exposure to a particular pesticide, especially in occupational agricultural workers. Clinical manifestations of chronic OP pesticide toxicity include nausea, vomiting, rhinorrhea, abdominal pain, dizziness, headache, fatigue, irritability, restlessness, depression, anxiety, somnolence, sleep disturbance, gait disturbance, limb pain, limb numbness, paresthesias and limb weakness.

Thailand is a developing country in which recent intensification of agriculture has led to an increase in the use of pesticides, especially OPs. It is of paramount importance that the impact of this increasing use of pesticides can be assessed and the information used to guide governmental and international bodies in the formulation of appropriate policies to evaluate adverse health effects.

In Thailand there is very little research relating to the monitoring of occupational OP exposure. In order therefore to increase awareness of the health concern, the present study was carried out to determine cholinesterase activity, pesticide exposure and health effects in an exposed agricultural population. Subjects exposed to OP pesticides were classified into subcategories to find out the effects of various factors on enzyme activities over the high- and low-exposure periods.

Subjects aged 25-35 years showed significantly higher BuChE activity than those with age <25 year over the high-exposure and the low-exposure periods. Individuals with increased exposure time (>10 years) also showed statistically lower BuChE activity than those with exposed time less than 5 years. Other factors, such as smoking habit and alcohol consumption did not affect these enzyme activities.

For the biological monitoring of OP exposure, the determination of cholinesterase enzyme activity is well known to evaluate the percentage of enzyme inhibition (% inhibition) at the high-exposure period with respect to that of the low-exposure period. AChE and BuChE activities showed -30 and -26% inhibition, respectively. Concurrently, these enzyme activities were compared between the control group and the exposed population. The results demonstrated that AChE activities in the high and low-exposure periods were significantly different from the control group. For BuChE activity, the exposed group also showed the statistically lower level for both periods (high-exposure period; 3.73 U/mL and low-exposure period; 4.91 U/mL) than those in the control group (5.96 U/mL).

From this study, the effect of OP exposure on cholinesterase activity was found predominantly in BuChE. One of the possible reasons is that potential inhibition of AChE and BuChE varies widely among the different OP compounds. Moreover, some OPs inhibit BuChE more strongly than AChE. For example, malathion, dizinon, chlorpyrifos and dichlorvos are stronger inhibitors of BuChE than AChE, in exposure to these substances, serum BuChE determination is a more sensitive indicator of exposure than AChE. In this study, chlorpyrifos and dichlorvos were the major OP compounds, which are likely to inhibit BuChE, as described above. However, in any individual, the onset, severity and duration of adverse health effects are mainly determined by the reaction potential of OPs, which is a function of chemical structure, concentration of OPs and period of time that OPs presented at the macromolecular target.

The results of this study suggested that long-term exposure of various organophosphate pesticides affected the cholinesterase activity and could lead to adverse health effects. Thus, monitoring of both AChE and BuChE activities, concurrent with the intervention programs such as the use of protective equipment as well as the knowledge of pesticide use, should be done to reduce and prevent health problems among the Thai agricultural population.

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***Source:*** International Archives of Occupational and Environmental Health, Vol. 82, No. 7, July 2009.




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