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The Stockholm Convention on Persistent Organic Pollutants

This treaty, brokered by the United Nations Environment Programme, banning the use of Persistent Organic Pollutants (POPs) will shortly come into force.

POPs are a group of very stable compounds that includes dioxins and the pesticide chlordane. They may accumulate in animals and plants at the end of the food chain, and have been linked to a range of human health problems.

From May 2004 the convention will ban the use of 12 types of pollutant. These compounds, however, are not of great commercial value. Chemical manufacturers of the 12 substances covered by the first phase of the convention have accepted that they pose a danger and have already phased out some of them.

Opposition is likely to come at later stages in the implementation of the convention when attempts are made to incorporate in the ban compounds that are currently made and sold in large quantities. These include brominated flame retardants such as hexabromocyclododecane (HBCD) and decabromodiphenyl ether (decaBDE), which meet some of the criteria for being classed as POPs.

Tens of thousands of tonnes of these compounds are made every year, primarily as flame-retarding additives for textiles, electrical equipment and building materials. The retardants can enter the environment during manufacture and disposal, and their stability means that they can build up in humans and animals over time.

However, environmental health researchers are still undecided on whether the current level of exposure to these compounds presents a health risk to people and animals.

The status of such contentious compounds will become clear when European Union nations complete a risk assessment of flame retardants later this year. The Bromine Science and Environment Forum, which represents bromine manufacturers, says that the industry is working with officials on this assessment and that, so far, the studies show no need for decaBDE or HBCD to be added to the convention.

Source: Environmental Health Perspectives Vol. 112 No. 1 2004.

Oxidant stress and the toxic effects of air pollution

Oxidant stress has emerged as a mechanism that underlies the toxic effects of most forms of air pollution, including particulate matter. Ambient particles are thought to carry redox-active metals and quinines deep into the respiratory organ where they overcome the lungs' antioxidant defences, the fluids that line the lungs. These fluids are rich in a range of enzymatic and non-enzymatic antioxidants.

Cells in the lung are also protected against oxidative stress by a similarly estensive range of intracellular defences, especially members of the glutathione S-transferase (GST) superfamily (*GSTM1, GSTT1,* and *GSTP1*). GST enzymes use a wide variety of products of oxidative stress as substrates and thereby have an important role in preventing the build-up of reactive oxygen species. *GSTP1* is strongly expressed in the respiratory epithelium and is the dominant GST in the lung, where it is thought to detoxify lipid and DNA oxidation products. *GSTM1,* also expressed in the lung, is mainly involved with detoxification of oxypolyacrylic hydrocarbons. Wide variations in GST activities have led to speculation about a genetic basis underlying individual susceptibility to oxidative challenge.

Now a research team from the University of Southern California has examined the nature of these variations.

Using a human nasalprovocation model, the team examined responses to allergen or allergen plus diesel-exhaust particles to assess whether functional variants in the GST superfamily could account for the variation in inter-individual responsiveness to diesel-exhaust particles. Individuals with *GSTM1*-null or *GSTP1* Ile105 wildtype genotypes showed enhanced nasal allergic responses to diesel-exhaust particles. Importantly, *GSTM1*-null individuals had a significantly larger increase in IgE and histamine in nasal lavage fluid after challenge with diesel-exhaust particles or allergen than children with a functional *GSTM1* genotype.

These new data help to increase our understanding of the effects of air pollution and its influence on allergic response at the cellular and molecular level and provide additional evidence supporting the concept of individual sensitivity to air pollution.

Source: The Lancet Vol. 363 Jan. 2004.

Current concern over brominated flame retardants

Brominated flame retardants (BFRs) have routinely been added to consumer products for several decades in a successful effort to reduce fire-related injury and property damage. Recently, concern for this emerging class of chemicals has risen because of the occurrence of several classes of BFRs in the environment and in human biota. The widespread production and use of BFRs; strong evidence of increasing contamination of the environment, wildlife, and people; and limited knowledge of potential effects heighten the importance of identifying emerging issues associated with the use of BFRs.

Worldwide, approximately 5,000,000 metric tons of bromine are produced each year, with a market value exceeding US $2 billion annually. Since 1975, the worldwide bromine demand has increased significantly, averaging a 2% growth rate between 1990 and 2000 [Organisation for Economic Co-operation and Development (OECD) 1994]. As of 2000, BFRs accounted for 38% of the global demand share of bromine, a stark increase compared with 8% in 1975. There are five major classes of BFRs: brominated bisphenols, diphenyl ethers, cyclododecanes, phenols, and phthalic acid derivatives. The first three classes represent the highest production volumes. In fact, five BFRs constitute the overwhelming majority of BFR production at this time, although new compounds are being introduced constantly as others are eliminated from commerce. The five major BFRs are tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCD), and three commerial mixtures of polybrominated diphenyl ethers (PBDEs), or biphenyl oxides, which are known as decabromodiphenyl ether (DBDE), octabromodiphenyl ether (OBDE), and pentabromodiphenyl ether (pentaBDE).

Hexabromocyclododecane (HBCD) is a nonaromatic, brominated cyclic alkane used primarily as an additive flame retardant in thermoplastic polymers with final applications in styrene resins. It has also been used, although to a lesser extent, in textile coatings, cable, latex binders, and unsaturated polyesters. Its total production is about 16,700 metric tons per year, making it a relatively minor contributor to the total BFR economy.

Poly brominated diphenyl ethers (PBDEs) potentially involve 209 different congeners, varying in both number and position of bromination. However, there appear to be many fewer actual PBDE congeners in commercial mixtures than the theoretical number possible, mainly because many of the congeners lack stability and tend to debrominate.

Although the production of PBDEs has continued to increase in the United States and Canada, voluntary bans have resulted in a declining use in Europe. DBDE represents the major product in all markets, accounting for approximately 80% of the total PBDE production worldwide. Unlike the other commercial products. DBDE is a relatively pure mixture, composed of $\geq$ 97% brominated diphenyl ether (BDE) 209 (DBDE), < 3% nonabromodiphenyl (NBDE), and small amounts of OBDE, DBDE is used as an additive flame retardant primarily in electrical and electronic equipment, as well as in textiles, where it is applied as a polymer backcoat to the fabric. Commercial OBDE is a more complicated mixture with several congeners present:

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ANTIBIOTICS AND BREAST CANCER

It has long been hypothesized that use of antibiotics may increase risk of cancer. However biological and epidemiological studies of this association are limited. An epidemiologic study of incident breast cancer in Finland found that women younger than 50 years who self-reported previous and/or present antibiotic use for urinary tract infection had an elevated risk of breast cancer compared with woman who had not used antibiotics.

Baseline bacteriuria was not associated with subsequent incidence of breast cancer, providing some assurance that antibiotic use, not the underlying infection, was the actual risk factor. Nonetheless, antibiotic exposure was measured only as a binary variable without consideration for antibiotic class, length of use, or use for conditions other than urinary tract infections.

Understanding whether an association between antibiotic use and breast cancer exists is particularly important given the high incidence of breast cancer and widespread antibiotic use in many countries. Breast cancer is the most frequently diagnosed nonskin malignancy and the second leading cause of cancer mortality in US women. It is also the most common cancer in women worldwide, with more than 1 million cases diagnosed each year.

A recently reported study carried out in the United States has found that among 2266 women with breast cancer, as compared with 7953 controls, the use of antibiotics was more common. Moreover, the risk of breast cancer was greater with longer duration of antibiotic use and was consistent across antibiotic classes. This finding is of particular concern since antibiotic exposure is common and sometimes nonessential.

The thoroughness of the study lends validity to the findings. Nevertheless, at the same time, the study methods give cause for certain concerns.

The authors appropriately chose an observational design, specifically a case-control study. Yet case-control studies have important limitations; a major one is confounding.

Confounding by indication occurs if women using antibiotics differ from nonusers in ways that elevate their breast cancer risk. Women with greater cumulative use of antibiotics were older, had earlier age at menarche, had higher body mass indexes, were more likely to have a family history of breast cancer, and were more likely to report postmenopausal use of hormones, all of which could have increased their risk of breast cancer. The authors adjusted for these factors and state that doing so did not materially influence their results. Nevertheless, the frequency of missing data, especially among controls, limited the validity of this adjustment. Residual confounding may have occurred, for instance, because physicians may have prescribed more antibiotics to women of upper socioeconomic status, who may have been more likely to adhere to preventive health recommendations such as routine mammograms. Indeed, women with a greater cumulative exposure to antibiotics tended (albeit nonsignificantly) to report educational attainment beyond high school. Furthermore, restricting the analysis to women who filled at least 1 antibiotic prescription reduced the size of the associations.

Beyond methodological considerations, the observed association, to be believable, must also be biologically plausible. The authors raise 2 mechanistic possibilities: antibiotics may reduce the capacity of intestinal microflora to metabolize phytochemicals that might protect against carcinogenesis; and tetracyclines stimulate prostaglandin E_2, implicating an overexpression of cyclooxygenase 2, the enzyme that synthesizes prostaglandin E_2 and that has been associated with mammary carcinogenesis. Along this same line of reasoning, antibiotics reduce commensural bacteria in the gut, and thus may lower the absorption of cholesterol. Cholesterol lowering has been associated with a reduced risk of breast cancer in some studies but with an increased risk in others.

However, a biological explanation based on mechanisms attributed to a given class of antibiotics is difficult to reconcile with the observation that the risk of breast cancer was elevated across multiple classes of antibiotics. Different antibiotics have different effects. Whereas tetracyclines stimulate prostaglandin E_2, presumably by mediation of cyclooxygenase 2, macrolides inhibit this pathway. With regard to microbiological mechanisms, antibiotic classes have various effects on intestinal microflora. For instance, in one study, phenoxymethylpenicillin had about half the effect on serum levels of the phytoestrogen enterolactone as did the macrolide class of antibiotics. Furthermore, sulfatrimethoprim and nalidixic acid have only a minor impact on intestinal microflora.

Another possible explanation for the association between use of antibiotics and risk of breast cancer is that antibiotics are an epiphenomenona marking chronic infection and chronic inflammation. Inflammation, induced by infections or irritants, has been linked to a substantial proportion (one sixth to one third) of incident cancers worldwide. Compelling evidence for a link between inflammation and breast cancer comes from preclinical and epidemiologic observations suggesting that nonsteroidal anti-inflammatory drugs (NSAIDs) protect against the development of breast cancer. In both animal and *in vitro* models NSAIDs inhibit mammary carcinogenesis, and in case-control and cohort studies use of NSAIDs reduces the risk of breast cancer by 22% overall and by 28% in frequent users with 10 or more years of exposure.

Reports of new associations, such as the present study, commonly provide more questions than answers.

Is the observed link between use of antibiotics and risk of breast cancer confounded by unmeasured factors? Is the effect due to use of antibiotics or to the indications for antibiotics? Does the link suggest caution in the use of antibiotics or suggest that infections at distant sites might promote inflammation localized to the breast? And, whether antibiotics are markers of inflammation or are themselves contributors to carcinogenesis, is use of antibiotics a risk factor for cancers at other sites? Time and further scrutiny will tell. While more research is needed, this study raises the possibility that long-term use of antibiotics may have harmful consequences, especially for patients for whom other therapeutic options are available.

Source: JAMA Vol. 291 No. 7 February 2004.

SEYCHELLES CHILD DEVELOPMENT STUDY ON THE EFFECTS OF EXPOSURE TO METHYLMERCURY

Eating fish is the main way most people are exposed to methylmercury, a neurotoxicant that in large doses causes mental retardation, seizures, cerebral palsy, and death. Because the fetal brain is particularly sensitive to methylmercury, the Seychelles Child Development Study was started in 1986 to ascertain the effects of low doses of methylmercury among 779 children living in these islands, whose mothers ate an average of 12 fish meals a week while pregnant.

The type of fish intake, and concentration of methylmercury in the fish, in the Seychelles, is similar to diets consumed during pregnancy in most of the world. After adjusting for key covariates, researchers have found a weak association between methyl mercury in maternal hair at the end of pregnancy and worse performance on one test of speed and coordination (non-dominant-hand grooved pegboard). However, performance on many other domains of cognitive performance (including dominant-hand grooved pegboard) was not associated with methylmercury concentrations in maternal hair. These investigators demonstrate convincingly that the association with the non-dominant test is almost certainly a chance finding. In addition, children of mothers with higher concentrations of methylmercury in their hair did better on ratings of hyperactivity than children of mothers with lower concentrations. The investigators conclude that data do not support the existence of a neurodevelopmental risk to young children from prenatal exposure to methyl mercury.

The Seychelles Child Development Study is a methodological advance over previous studies, despite limitations that its investigators acknowledge. In addition to studying a population whose fish diet is generalisable to most parts of the world, the researchers carefully measured a wide range of variables that might affect cognitive-behavioural development, including social and environmental modifiers of development (e.g., home environment, maternal age), and the concentration of methylmercury in the child's hair well after birth (this is a key measurement). As expected, all such variables had much stronger effects on the cognitive-behavioural assessments than did prenatal exposure, which had no measurable effect.

On balance, the existing evidence suggests that methylmercury exposure from fish consumption during pregnancy, of the level seen in most parts of the world, does not have measurable cognitive or behavioural effects in later childhood.

Source: The Lancet, Vol. 361, May 2003.

Antioxidant properties of algae and their effectiveness against methylmercury induced toxicity

In a number of research studies, several lines of evidence illustrate the diversity of perturbations induced by methylmercury (MeHg). The neurotoxic effects are well documented at the clinical level, but the biochemical and molecular mechanisms of Me Hg action in mammalian cells are still a matter of debate. However, a growing body of research evidence suggests oxidative stress as part of the toxicity mechanism of MeHg in cell cultures and animal models. This has led to an examination of the use of algae and microalgae as sources of anti-oxidative preparations which could have important biomedical applications.

A recent study has examined the effect of an aqueous extract from the marine seaweed *Halimeda incrassata* (Hi) against the oxdative stress induced by MeHg on in vitro and in vivo models. In GTI-7 mouse hypothalamic cell cultures, the extract of Hi increased cell viability and reduced ROS production after 24-h exposure to methylmercuric chloride (MeHgCl). Wistar rats, acutely intoxicated with MeHgCl, had reduced levels of serum and brain thiobarbituric reactive substances when treated with the Hi extract. Similarly, animals exposed to repeated doses of MeHgCl were protected by the seaweed extract from variations in body weight, food consumption and the appearance of neurological effects. This research supports the notion that oxidative stress is directly involved in MeHg intoxication, so that natural antioxidants, particularly those in the extract of Hi, can be useful therapeutic alternatives.

Source: Veterinary and Human Toxicology 46, February 2004.

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approximately 10-12% hexabrominated diphenyl ethers (HxBDE), 44% heptabrominated diphenyl ethers, 31-35% OBDE, 10-11% NBDE, and <1% DBDE (WHO 1994). It is not clear whether any pentaBDEs are present in the commercial OBDE products. OBDE is a minor PBDE product, used as an additive in polymers for use in plastic housings and smaller components, such as office equipment.

Overall the BFRs represent major industrial chemicals whose use has increased dramatically over the past few decades. They are produced to prevent fires and thus can have a direct and obvious benefit. However, concerns are being raised because of their persistence, bioaccumulation, and potential for toxicity, both in animals and in humans. Production and use patterns are different in various parts of the world. There is clearly a need for more systematic environmental and human monitoring to understand how and where these chemicals are being released into the environment, and what is happening to them once they enter the environment.

Source: Environmental Health Perspectives Vol. 112 No. 1 2004.

Blood Lead Concentration and Essential Tremor : the Role of Environmental Toxicants

Essential tremor (ET) is a neurologic disease that is characterized by an action tremor of the hands and/or head. Patients also may have signs of more widespread cerebellar involvement, abnormalities referable to the basal ganglia, and cognitive deficits. ET is considered to be distinct from age-related enhanced physiologic tremor, which has different clinical and electrophysiologic features. The disease is highly prevalent in the general population (1-6%) and occurs in all populations studied to date. The prevalence increases with age. Estimates of the prevalence in individuals who are in their sixties and seventies have been as high as 20.5%. As such, ET is one of the most common neurologic diseases.

The pathogenesis of this progressive and often disabling disease is poorly understood, although there is evidence of cerebellar involvement. There is no cure for ET, and there has been no attempt to favorably modulate or halt its progression with neuroprotective therapy. Medical treatment merely aims to lessen the severity of the tremor, which is the major symptom, and the first-line medications are ineffective in up to 50% of patients.

Although genetic susceptibility is an important determinant of disease etiology, it has been hypothesized that nongenetic factors (i.e., environmental factors such as toxicants) could contribute to disease etiology in many cases. The identification of these factors is a critical step in disease prevention, yet they have received little attention.

Lead is a ubiquitous toxicant, and laboratory animals and humans exposed to high levels of either inorganic or organic forms of lead develop neurologic disorders in which action tremor is prominent. Destruction of cerebellar Purkinje cells is a major feature of the pathology of lead toxicity. The effect of chronic, low-level exposure to lead has been linked with developmental problems, deficits in intellectual performance and decreased stature in children, and poorer performance on cognitive tests in adults.

In a recent case-control study, it was found that the blood lead *(BPb)* concentration was higher in ET patients than in controls. This association between higher BPb concentration and the diagnosis of ET persisted after adjusting for confounding variables. The association was strongest in patients with sporadic ET, that is, those with no family history of tremor, suggesting that lead as a toxicant might be of more relevance in ET patients without a genetic susceptibility for ET. The prevalence of lifetime occupational exposure to lead was similar in ET patients and controls, suggesting that the higher BPb concentration in ET patients was not due to increased risk of occupational exposure. However, the prevalence of occupational lead exposure was very low in the study population; thus, occupational lead exposure as a risk factor for ET cannot be excluded.

Although the data demonstrate an association between ET and higher BPb concentration, one must be cautious about the interpretation of these data. It is unlikely that a BPb concentration of 3.3 µg/dL alone is sufficient to cause ET. If this were so, the prevalence of ET might be higher than 1-6%. An incidence study is needed to directly address the issue of whether higher BPb concentrations precede or follow the diagnosis of ET. Second, a study of bone lead concentration is required because this is a better measure of cumulative exposure to lead than are BPb concentrations. These types of studies are needed before a chelation trial, to try to modify the subsequent progression of the disease (i.e., worsening of tremor) among ET cases.

Humans may be exposed to both inorganic and organic forms of lead from occupational and nonoccupational sources. In humans and rats, lead exposure may lead to acute and chronic progressive disorders in which action tremor is a prominent feature. There is also evidence that lead toxicity causes cerebellar pathology. Rat pups fed a diet containing 4% lead acetate demonstrated changes in the topology of Purkinje cell dendritic trees due to change in Purkinje cell metabolism. Perinatal exposure to inorganic lead results in degenerative changes in Purkinje cells in the rabbit cerebellum. Inorganic lead exposure causes a reduction in the total number of cerebellar cells in developing rat brains. Moreover, an autopsy study of humans with chronic organic lead exposure revealed severe destruction of cerebellar Purkinje cells. Multiple lines of evidence suggest that the cerebellum is involved in ET, including imaging studies, positron emission tomography, functional magnetic resonance imaging, and magnetic resonance spectroscopic imaging, clinical studies and electrophysiologic studies case reports. Unfortunately, there have been few postmortem studies of ET; several studies revealed loss of cerebellar Purkinje cells, but without control brains for comparison, these results are difficult to interpret.

Source: Environmental Health Perspectives Vol. 111 No. 4 2003.

CASE – CONTROL STUDY OF BLADDER CANCER AND ARSENIC IN DRINKING WATER IN THE WESTERN UNITED STATES

Several populations in the United States have been exposed to arsenic-contaminated drinking water at levels near 100 µg/liter. However, since there is little information on the cancer risks at these levels, risk estimates for these exposures have involved extrapolations from the results of studies from highly exposed populations in Taiwan. Such extrapolations have suggested that the cancer risk from drinking water containing arsenic at 50 µg/liter may be as high as one in 100. Many different models have been used in these extrapolations, and differences in the models have led to large disparities in estimated risk. These disparities have fueled controversy and uncertainty in the low dose risk estimation process, highlighting the importance of actual studies at low exposures. According to the 1999 National Research Council Subcommittee on Arsenic in Drinking Water, additional epidemiologic evaluations are needed to characterize the dose-response relationship for arsenic-associated cancer and noncancer endpoints, especially at low doses. Such studies are of critical importance for improving the scientific validity of risk assessment.

Thus, a recent study has been carried out to investigate bladder cancer risk using a case control study design in populations in the western United States exposed to low to moderate arsenic levels in drinking water.

The study area consisted of six counties in western Nevada and Kings County in California. The cities of Hanford. California, and Fallon, Nevada, which comprise 21 percent of the current population of the study area, have historically been the two largest populations in the United States exposed to drinking water arsenic near 100 µg/liter. Other parts of the study area have substantially lower arsenic levels, thus offering a marked contrast in exposure.

Cases were subjects aged 20-85 years, with primary bladder cancer first diagnosed between 1994 and 2000, who lived in the study area at the time of diagnosis. Lists of subjects meeting these criteria were provided by the Nevada Cancer Registry and the Cancer Registry of Central California. Completeness of case ascertainment for the Nevada Cancer Registry has been estimated at 94.5 percent for the years 1995 and 1996. Completeness for the Cancer Registry of Central California has been estimated at 95 percent. In Nevada, rapid case ascertainment, involving hospitals and physicians, was used to ascertain cases for the last 3 years of the study period. All pathology laboratories and associated hospitals in the study area and in Reno, Nevada, the nearby referral area, participated in rapid case ascertainment.

Controls were frequency matched to cases by 5-year age group and gender. Controls with a history of bladder cancer were excluded.

Arsenic measurements for all community-supplied drinking water within the study area were provided by the Nevada state Health Division and the California Department of Health Services.

Most of the remaining public water supplies in the study area contain less than 10 µg of arsenic per liter, although a few small cities have public water supplies with arsenic levels between 10 and 50 µg/liter. Most private wells in the study area contain arsenic below 10 µg/liter, although levels in private wells near Fallon and Hanford vary dramatically, from 0 to over 1,000 µg/liter.

A total of 265 bladder cancer cases were identified during the study period. Fifteen of these had primary residences outside the study area at the time of diagnosis. Of the 250 who remained, 181 (72 percent) were interviewed, 30 (12 percent) declined participation, 30 (12 percent) could not be located, and 10 (4 percent) were not interviewed because of language issues or illness.

Overall, no clear association was identified between bladder cancer risk and the exposures found in the study area. Interestingly, the overall risks were below those predicted using data from highly exposed populations in Taiwan. This study, however, provides some evidence of elevated relative risks for bladder cancer in smokers exposed to drinking water arsenic at levels near 200 µg/day.

Source: American Journal of Epidemiology, Vol. 158, No. 12, 2003.

MUTAGENIC ACTIVITY OF AIRBORNE PARTICULATE POLLUTANTS

Urban air is contaminated by gaseous and particulate emissions from a variety of sources. Emissions emanate from vehicles, industries, and power stations and also occur naturally. These emissions, as well as their atmospheric transformation products, damage ecological systems and adversely affect public health. Airborne particles have been a particular concern because epidemiological findings link current levels of airborne particulate pollutants to a growing list of adverse health effects.

Now researchers in the United States have presented experimental evidence that airborne particles cause heritable genetic changes in the male mouse germline that can be passed on to the next generation.

By monitoring changes in the size of noncoding tandem-repeat DNA sequences, the researchers have shown that offspring of mice exposed to an industrial location on western lake Ontario have an increased rate of presumptive mutations and that these genetic changes are paternally derived.

Their discovery that the mutation rate could be reduced by ~ 50% by cleansing the air with a high-efficiency-particulate-air (HEPA) filter suggests that particle-bound mutagens, or the particles themselves, are responsible for the observed, heritable DNA changes. These new findings extend a series of investigations that began with the observation that herring gulls in

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MUTAGENIC ACTIVITY OF AIRBORNE PARTICULATE POLLUTANTS

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Hamilton Harbor, Ontario, have a higher rate of minisatellite DNA changes than gulls in rural sites. A follow-up experiment with mice showed increased induction of DNA changes in the offspring of mice housed in a polluted location at the harbor compared with control animals housed in an unpolluted location.

Urban air pollution is known to have mutagenic activity associated with airborne particles linking it to lung cancer

Multiple chemicals, such as polycyclic aromatic hydrocarbons (PAHs), contained within particles or bound to their surfaces are mutagens or carcinogens. Small inhaled particles, which are cleaned from the air by a HEPA filter, penetrate deeply into the lungs, where adsorbed materials enter the blood and become distributed systemically. PAH exposure, whether from tobacco or coal emissions, leads to the formation of lung tumors carrying unique sets of mutations. Thus, inhaled combustion emissions and possibly, polluted urban air, generally induce mutations in somatic cells.

Mechanisms for inducing changes in tandem-repeat DNA sequences lie outside the conventional model for the induction of mutations in coding genes and are poorly understood. Changes in these DNA sequences occur at rates much higher than predicted on the basis of mutation rates in coding genes. PAHs bound to particles are a candidate group of chemicals that react with DNA after metabolic activation. PAHs are a component of emissions from steel mills and vehicle exhaust, primary sources of air pollution in the contaminated Hamilton Harbor location, and they cause germ cell mutations in mammals. PAHs such as benzo(a)pyrene and dimethylbenzanthracene induce dominant lethal mutations in female mice when given by intraperitoneal injection, an exposure route of uncertain relevance to inhalation.

New evidence shows that PAHs associated with inhaled particles also may cause changes in humans during development. Pregnant women exposed to elevated levels of particulate matter and carcinogenic PAHs in ambient air have an increased risk of delivering a low-birth weight child compared to women with lower exposures. This risk is doubled if the exposure occurs during the first month of pregnancy. A link also exists between somatic mutation in newborns and transplacental exposure to common air pollutants, including polycyclic organics. Studies in humans indicate that elevated air pollution also may cause DNA damage in male germ cells. Evidence on cigarette smoking, another source of exposure to PAHs, suggests the possibility of smoking-associated germ cell mutations.

Source: Science Vol. 304, 2004.

PRENATAL TOXINS MAY TRIGGER PSYCHIATRIC DISEASE

There is much evidence that toxins such as lead and alcohol can harm a mother's unborn child and trigger developmental problems during childhood. Now US researchers have carried out a study which indicates that babies exposed to lead in the womb may be at increased risk of developing schizophrenia as adults. This new study is one of the first to show that this damage can precipitate disorders that take years to manifest themselves. Schizophrenia, for example, is usually not diagnosed until an adults' late teens or early twenties. The US study has compared the blood lead levels of 44 women whose children went on to develop schizophrenia with 75 others whose children did not. The offspring of mothers whose blood showed in excess of 150 micrograms of lead per liter were twice as likely to go on to develop schizophrenia as those whose blood levels were below this threshold.

Researchers suspect that lead may kill nerve cells in a fetus's growing brain but they are unsure exactly how lead causes injury.

Whereas the samples were collected between 1959 and 1966 when lead exposure in California, where the study was carried out, was relatively high because of the use of leaded gasoline, most petrol today is unleaded.

However, lead still leaches into the environment from industrial smelters and paint, and thus might still account for a significant number of schizophrenia cases in developing countries.

In the past few years, animal research has shown that drugs that dampen brain-cell activity – such as alcohol, certain anaesthetics and anti-epiliptic drugs – prompt cells to commit suicide. Brain cells are thought to be particularly vulnerable from mid-pregnancy through the first two or three years of a baby's life.

Even a single dose of alcohol or some anaesthetics can wipe out a swathe of nerve cells in this way.

A blood alcohol level equivalent to that after a couple of cocktails, maintained for just half an hour or more, can double or quadruple the number of brain cells dying off in a mouse's growing fetus. It is not yet known if alcohol has the same effect in humans.

Researchers plan to examine whether fetuses exposed to alcohol or other drugs are also at increased risk of schizophrenia or other psychiatric disorders as adults

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Source: Online January 2004 at http://dx.dol.org/.

COFFEE CONSUMPTION AND RISK FOR TYPE 2 DIABETES MELLITUS IN U.S. ADULTS

Over the last 20 years, there has been a dramatic increase in the prevalence of type 2 diabetes mellitus in the United States where the disease now affects approximately 8% of the adult population. Short-term metabolic studies have suggested that caffeine adversely affects insulin sensitivity and glucose metabolism indicating that coffee consumption may be related to diabetes. In the United States, coffee consumption is widespread; more than 50% of Americans drink coffee and average per capita intake is 2 cups per day.

In humans, acute administration of caffeine decreases insulin sensitivity and impairs glucose tolerance. On the other hand, caffeine stimulates thermogenesis and increases energy expenditure, which may facilitate weight reduction and maintenance. Because of these complex physiologic effects of caffeine and because tolerance to the humoral and hemodynamic effects of caffeine typically develops with long-term use, it is difficult to extrapolate findings from short-term metabolic studies to long-term use of coffee and other caffeinated beverages.

A recent epidemiologic study has found a statistically significant inverse association between coffee consumption and risk for type 2 diabetes in a sample of Dutch participants. After adjustment for potential confounders, the relative risk for type 2 diabetes among participants consuming a least 7 cups of coffee per day as compared with those consuming 2 cups or less per day was 0.05 (95% CI, 0.35 to 0.72; $P<0.001$ for trend). The study, however, could not distinguish regular coffee from decaffeinated coffee and did not evaluate the association with total caffeine intake.

A recently published longitudinal U.S. study has examined long-term intake of coffee and other caffeinated beverages and decaffeinated coffee in relation to incidence of type 2 diabetes in 2 large prospective cohorts of men and women, examining particularly whether the associations were modified by smoking and body mass index. The authors of the study followed 41, 934 men from 1986 to 1998 and 84, 276 women from 1980 to 1998, and found a statistically significant inverse association between coffee intake and risk for type 2 diabetes.

In these 2 large prospective cohorts of men and women, a statistically significant inverse association between coffee intake and risk for type 2 diabetes was found. These data are broadly consistent with the recent epidemiolomic study of 17 111 Dutch men and women 30 to 60 years of age. The U.S. study, however, with a much larger sample size and longer follow-up, has extended the results of the Dutch study by examinging the effects of total caffeine and different types of coffee. The study has found a modest inverse association between higher consumption of decaffeinated coffee and diabetes risk, but no statistically significant association was observed for tea consumption.

These prospective data suggest a statistically significant inverse association between intakes of caffeine and regular coffee and incidence of diabetes in both men and women. This association is independent of body mass index, cigarette smoking and other dietary and life-style factors. However, this observational study cannot prove a cause-effect relationship, and it is premature to recommend increased coffee drinking as a means to prevent type 2 diabetes. Further metabolic studies are required to investigate long-term effects of caffeine on glucose homeostasis, insulin resistance, and energy expenditure.

Source: Annals of Internal Medicine, Vol. 140, No. 1, January 2004.

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