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Study of Wild City Pigeons as an Indicator Species for Monitoring Air Pollution in Urban Areas

Epidemiological studies have shown an increase in respiratory diseases such as bronchitis and an increase in the incidence of lung cancer in human populations in urban areas as compared with populations in rural areas, underlining the health risks from air pollution caused by vehicle discharge and industrial activities.

Concern over the potentially mutagenic and carcinogenic effects of air pollutants has resulted in numerous studies of the mutagenic activity of extracts of particles of airborne pollutants. However, less attention has been paid to the ecological impact of air pollutants since it is difficult to find suitable biological indicators for areas with high traffic density where the impact of vehicle discharge is most severe. A recent study, carried out in the Netherlands, of the possible relevance of pigeons as an indicator species for monitoring air pollution, is therefore of particular interest. This study was conducted to determine the levels of polycyclic aromatic hydrocarbon (PAH)-DNA adducts, oxidative DNA damage and heavy metal residues in tissues of wild city pigeons in locations of high and medium traffic density, on the assumption that air pollution increases as the traffic density increases.

Particulate air samples were taken at four different locations and analyzed for PAH and metal concentrations in order to establish the relevance of pigeon dosimetry as a biological indicator of urban air pollution.

In the total of 29 wild city pigeons used in the study and caught in four different locations with varying traffic density, levels of PAH-DNA adducts, oxidative DNA damage, and heavy metal residues were determined in kidney, lung, liver and blood. The contribution of leaded gasoline to total

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Study of Wild City Pigeons as an Indicator Species for Monitoring Air Pollution in Urban Areas

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body lead content was estimated by measuring concentrations of Pb and its isotopes in blood.

The study showed that the highest lead and cadmium concentrations in blood, kidney, liver and lung were found in the locations with highest density of traffic. The first results of the study indicate that pigeons can be used for biomonitoring of exposure to heavy metals. The most striking findings in the Netherlands study are the regional differences of lead and cadmium pollution as reflected in body load of the pigeon. Moreover, the contribution of lead from gasoline, determined on the basis of the Pb isotopic composition in blood, also revealed marked regional differences.

Source: Environmental Health Perspectives, Vol. 105, No. 3, March 1997.

Biomarkers in Environmental Applications

The use of biomarkers in the assessment of environmental health both in the workplace and in the ambient atmosphere is of great importance. In broad terms, a biomarker can be any measurement in or from biological material that defines an exposure or a response to that exposure. Biomarkers have been classified into three subtypes:

exposure – measurement of the parent compound, metabolite, or unique response attributable to a compound or a group of compounds.

effect – a quantifiable response of an organism that can be directly linked to exposure.

susceptibility – any factor that can vary from individual to individual that could alter the formation or metabolism of the compound or any intermediate and biological response.

The biomarkers most generally recommended for the most common air pollutants are as follows:

Aromatics.

Blood benzene is the most sensitive biomarker for recent, short-term exposure (2 hr). Breath levels also correspond to recent, short-term exposure (2 hr) and are better for subject compliance. Mercapturic acid in urine reflects whole body metabolism and integrates exposures over a longer period (a few hours). Blood protein adducts integrate exposures over a much longer period (weeks to months).

1, 3-Butadiene.

Air concentrations of butadiene should be used for routine assessment of exposure. Charcoal tubes and air pumps, or passive absorbent technologies are fairly well established for this purpose. For unanticipated accidental exposures and to determine the relationships between external exposure and internal dose, use exposure markers. To address the relationship between internal dose and effect of dose, to investigate mechanistic issues, and for risk assessment, use effect biomarkers.

Polycyclic Aromatic Hydrocarbons.

Assays for 1-hydroxypyrene should be incorporated into studies to acquire information about the degree of exposure to PAHs.

Metals.

Protein-DNA cross-links should be used to assess chromium exposure. For manganese, the presence of the metal in urine and red blood cells is diagnostic, but magnetic resonance imaging (neurological exam) should be included for suspect populations of manganese exposure.

However, there are major gaps in our knowledge of biomarkers in environmental applications. These gaps will, perhaps, be best filled by concerted efforts to link different biomarkers to exposure and health effects, rather than by studies that focus on only one biomarker. An important issue in this regard is that of biomarker validation in humans and the low levels of exposures that occur in the general population. Some biomarkers are only formed at high exposure concentrations because of different metabolic pathways operating at different exposure concentrations, and controlled human studies with most of the air toxics are not possible. Thus creative approaches need to be developed and the following priorities observed:

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β-carotene and Cancer

The prospect that a high consumption of certain vitamins may offer protection against cancer has stimulated much research interest. The compound β-carotene, in particular, has been most intensively studied in recent years with regard to possible cancer prevention properties.

β-carotene is one of the few carotenoids that has pro-vitamin A activity and it is the carotenoid that is most efficiently converted to retinol in the human body.

The mechanisms through which retinol and its esters may influence carcinogenesis have been hypothesized to include an action on the cell nucleus, involving the expression of the genetic information controlling cell differentiation. Specific binding proteins are believed to be responsible for the transport of retinol and retinoic acid within the cell and across the nuclear membrane, suggesting a hormone-like control of cell differentiation. Retinol has a variety of effects on the cell membrane involving altered glycoprotein synthesis and changes in membrane receptors for various hormones. The action on these receptors may influence cell to cell interactions, cell adhesion, and cell membrane permeability. Also, animal studies have shown that retinol increases both the humoral and cell mediated hormone response and could thus enhance immune surveillance in tumorigenesis.

Thus, with regard to cancer prevention, it has been hypothesized that β-carotene may be beneficial through local conversion to retinol at tissue level.

A large number of observational epidemiological studies have investigated the association between β-carotene intake or status with cancer risk in humans. These almost 100 case control and cohort studies have recently been reviewed.

The results of both case-control and cohort studies show a remarkable consistency for the association of increased lung cancer risk with low levels of dietary β-carotene or low plasma β-carotene levels. For stomach cancer, the evidence is also consistent, though the number of studies is more modest. For breast and prostate cancer, the studies indicate no consistent association of plasma or dietary β-carotene and reduced cancer risk. For colorectal cancer, the effect will be moderate, if existent. The epidemiologic studies should be carefully interpreted, since dietary habits may be misclassified and smoking may reduce plasma β-carotene levels. Also, observational epidemiology cannot definitively resolve whether associations are indeed due to ß-carotene, or to other components in ß-carotene rich fruits and vegetables.

The first results of human intervention studies on β-carotene cancer incidence are now becoming available. A combination of β-carotene, vitamin E and selenium reduced stomach cancer mortality in China. On the other hand, the results indicate a lack of protective effect of β-carotene on lung cancer in smokers with 30-35 years smoking history in Finland, colorectal adenoma in the USA and second skin cancers in the USA. However, these trials had a relatively short follow-up (5-7 years) and may only provide information on the absence of the efficacy of ß-carotene in the very late stages of carcinogenesis.

Since many of the observational studies had a very long follow-up, this may imply that intervention studies may also need a long follow-up to establish beneficial effects in earlier stages of carcinogenesis. It can be expected that the results of other ongoing trials and continued follow-up will provide more experimental data on the efficacy of β-carotene.

Source: Cancer Letters 114, 1997.

Biomarkers in Tea and Cancer Research

The health-promoting actions of tea have been explored through epidemiologic and marker studies. From these studies, tea drinkers would seem to have a lower risk of heart disease and several types of cancer. Experimental research in laboratory animals has demonstrated inhibition of carcinogenesis at a number of organ sites. These laboratory approaches provide tools to explore the underlying mechanisms related to nutritional carcinogenesis in humans. In current research studies, a great number of biomarkers are used in cancer research. In general, surrogate markers for carcinogenesis are most meaningful if they are closely linked to the causal pathway or if they are strongly associated with the genotypic character of the neoplastic cell. Selection of appropriate biomarkers needs to take account of the proposed anticarcinogenic mechanism attributed to the putative protective compound. In the case of both green and black tea and their constituent polyphenolic substances, considerable current evidence would seem to indicate cancer protection during the early stages of carcinogenesis.

Since there is a need for more definitive studies with humans, particular consideration should be given to

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Menstrual Cycle Ovarian Cancer Link

Researchers at Duke University Medical Center in the United States have completed a study which explains the statistical link between the risk of ovarian cancer and a woman's lifetime number of ovulations, or menstrual cycles. A high number of ovulations can increase by nine times the chances of producing cells with a genetic flaw that often leads to ovarian cancer.

The study shows that a high number of ovulations increases the chances a tumor suppressor gene p53 can be mutated. The majority of ovarian cancers have this p53 mutation.

However, anything that lowers the number of lifetime ovulation cycles such as giving birth and nursing a new born reduces the risk of ovarian cancer. The study indicates that birth control pills, which control ovulation, serve also to protect against ovarian cancer.

News item.

Developing Therapies for Parkinson's Disease

Research into the causes of Parkinson's disease is of the greatest importance because of the inadequacy of the drugs currently used in the treatment of the disorder. A better understanding of the nature of the disease process is necessary in order to find more effective therapeutic agents. It is now known that the traditional medication of extracts of the deadly nightshade plant works by inhibiting the activity of acetylcholine in the striatum, the region of the brain adjoining the substantia nigra. Acetylcholine is one of the chemical molecules that carries messages between neurons. Scientists came to understand that dopamine released into the striatum was needed, at least in part, to counteract the effects of acetylcholine. In the absence of such moderation, acetylcholine overexcites striatal neurons that project to higher motor regions of the brain.

In the 1960s the drug levodopa, or L-dopa, was developed specifically to compensate for the decline of dopamine in the brain of patients with Parkinson's disease. Dopamine itself cannot be used as a drug because it does not cross the blood-brain barrier- the network of specialized blood vessels that controls which substances will be allowed into the central nervous system. However, L-dopa crosses the barrier readily. It is then converted to dopamine by neurons that survive in the substantia nigra and by nonneuronal cells, called astrocytes and mircroglia, in the striatum.

Although it was an important breakthrough in the treatment of patients with Parkinson's disease, it has been found over time that it does not provide an effective cure, and the quest still continues for additional, more effective therapies.

One notion that has been explored in recent research is that oxidation could help account for Parkinson's disease. A number of studies have shown that a synthetic toxin sometimes used in scientific experiments could cause parkinsonian symptoms in animals and that it worked by inducing the death of dopamine-producing neurons in the substantia nigra. This toxin poisoned the neurons by inducing formation of at least two types of free radicals. The part of the substantia nigra that deteriorates in Parkinson's patients contains above-normal levels of substances that promote free radical formation (a notable example is iron). At the same time, the brain tissue contains unusually low levels of antioxidants, molecules involved in neutralizing free radicals or preventing their formation.

It has been demonstrated that iron, regardless of its source, can react with dopamine and its derivatives in at least two ways that can further increase free radical levels in dopamine-synthesizing cells.

In one set of reactions, iron helps dopamine to oxidize itself. Oxidation of dopamine converts the molecule into a new substance that nigral cells use to construct their dark pigment, neuromelanin. When iron levels are low, neuromelanin serves as an antioxidant. But it becomes an oxidant itself and contributes to the formation of free radicals when it is bound by transition metals, especially iron.

In the other set of dopamine-related reactions, iron disrupts the normal sequence by which the neurotransmitter is broken down to inert chemicals. Neurons and microglia usually convert dopamine to an inactive substance and hydrogen peroxide, the latter of which becomes water. When iron is abundant, though, the hydrogen peroxide is instead broken down into molecular oxygen and a free radical. Dopamine's ability to promote free radical synthesis may help explain why dopamine-making neurons are particularly susceptible to dying from oxidation. This ability has also contributed to suspicion that L-dopa, which increases dopamine levels and eases symptoms, may, ironically, damage nigral neurons.

Although research to date has revealed few clues as to the initial causes of Parkinson's disease, it has provided ideas for new therapies aimed at blocking oxidation or protecting neurons in other ways. However, the true aim of therapy must ultimately be to identify the disease process long before symptoms arise, so that therapy can be given in time to forestall the brain destruction that causes patient's discomfort and disability. This remains a challenge for the future.

Source: Adapted from Scientific American, January 1997.

Occupational Risk from Exposure to Metals

Parkinson's disease is an idiopathic neurodegenerative disorder that produces slow body movement, muscular rigidity, limb tremor and loss of balance. Researchers from the Henry Ford Hospital, Detroit, USA, have found that exposure to manganese or copper in the workplace could be a cause of the disorder. Their study has also found that people exposed to combinations of lead and copper, lead and iron, or iron and copper for more than 20 years are more likely to get the disorder than people exposed to only one of the metals.

The findings suggest that a combination of selected metals may act together to increase the risk of Parkinson's disease. The study raises the question of whether cumulative substantia nigra neuronal injury and death occurs in some patients because of such exposures.

The biological mechanisms that could account for neurotoxicity of these metals in Parkinson's disease, either individually or in combination, have not as yet been established.

The importance of the Detroit study is that it is the first to link two or more decades of occupational metal exposures with any chronic neurodegenerative disorder. The findings of the study thus emphasize the potential importance of the chronic neurotoxicity of metals and the need for vigilance in monitoring chronic metal exposure in the workplace.

Source: Neurology, Vol. 48, 1997.

DETOXIFICATION OF MERCURY

Reduction of the toxicity of mercury by coadministration with selenium (Se) is explained by the formation of a complex between a specific plasma protein and the two elements, which are bound to the protein at an equimolar ratio.

A study carried out in Japan characterised the specific binding protein in order to clarify the detoxification mechanism. In the study, the coadministration of ^{82}Se-enriched selenite and mercuric chloride into a rat produced a selenium and mercury binding peak on a gel filtration column as measured by high-performance liquid chromatography with detection by inductively coupled argon plasma-mass spectrometry. The specific binding protein was also detected *in vitro* by incubating ^{82}Se-enriched selenite and mercuric chloride in serum in the presence of glutathione.

In the present study, the formation of the equimolar complex of the two elements occurs first, and then the complex binds to the specific plasma protein to form the highly stable complex. The formation of the stable complex seems to be related to the detoxification mechanism of selenium against mercury.

Source: Toxicology and Applied Pharmacology 143: 274-280, 1997.

Mercury Content in Skin-lightening Creams

Skin-lightening creams containing inorganic mercury are widely used by dark-skinned people to obtain a lighter skin tone. The degree of absorption and excretion of mercury following exposure is directly dependent on the amount of the metal in the base. Both organic and inorganic mercurials are used in topical cosmetic preparations with organic forms such as phenyl mercuric acetate being used as cosmetic preservative and inorganic forms such as ammoniated mercury constituting the active ingredient in skin-bleaching creams. It is well known that chronic exposure to either inorganic or organic mercury can lead to permanent damage of the brain, kidneys and developing fetus. The most sensitive target of low-level exposures to metallic and organic mercury appears to be the nervous system, whereas the kidney is the most sensitive target of low-level exposure to inorganic mercury.

In the use of skin-lightening creams containing inorganic mercury, mercury is absorbed through the skin and concentrates in the kidney, mainly in the tubular region. Studies have shown that it is possible to induce permanent dysfunction by exposure to nephrotic chemicals during prenatal periods. The exposure of placental cells to mercury causes accumulation of the metal in the placental membrane and lowers the membrane fluidity; this may affect membrane function and cause damage to the developing fetus. Inorganic mercury can also be excreted into the mammary glands.

A recent study of 38 skin-lightening cream samples obtained from local markets in Saudi Arabia, where use of such preparations by women is common, revealed that 17 of the creams contained mercury levels above the 1 ppm level established as permissible by the U.S. Food and Drug Administration (FDA). Four of the samples were found to contain over 1000 ppm of mercury.

Source: Journal of Toxicology and Environmental Health, 51: 123-130, 1997.

An Ecological Study of Cancer Risks in Communities Adjacent to Petrochemical Plants

In a number of studies, high mortality rates from various cancers have been found among workers in the petroleum and petrochemical industries. However, comparatively few studies have examined the relationship between exposure to petroleum and petrochemical emissions and cancer risk for communities that live close to petrochemical plants.

In Taiwan, an ecological study has been conducted to evaluate whether cancer risks are associated with residence in communities adjacent to petroleum or petrochemical industrial pollution. In this study the mortality rates from various cancers between 1982 and 1991 in areas of Taiwan where the petroleum or petrochemical industry is most heavily concentrated were compared with the rates in other areas with similar sociodemographic characteristics but with no involvement in the petrochemical industry. Taiwan is divided into 361 administrative counties. According to a 1989 census, 218 counties had plants engaged in petrochemical manufacturing, although there were less than 50 employees in about 30% of the plants in these counties.

In the present study, an individual county was classified as a "petrochemical industrial county" (PIC) if the number of workers in petroleum and petrochemical plants comprised at least 2% of the county's total population. The proportion was used as an indicator of a resident's exposure to air emissions from petrochemical plants. In all, 19 counties satisfied these criteria.

Each PIC was matched with one reference county with regard to level of urbanisation and differences in percentage of petrochemical workers and workers in nonpetrochemical industries.

Information was collected concerning both number of deaths and midyear population by sex and age per calendar year from 1982 to 1991 in petrochemical and reference counties. In Taiwan, the International Classification of Disease, Injury and Causes of Death is used to code the cause of death, and the system has been computerised since 1972.

Average annual cancer mortality rates per 100,000 population were calculated for males and females for each of the petrochemical and reference counties from 1982 to 1991. As the age distribution was not comparable among the PIC and reference counties, the age-standardised rates were computed using the world population in 1976 as the standard population.

The present study, spanning a ten year period, did not find significant relationships between residence near petrochemical industries and cancer mortality. However, the authors of the study point out that their ecological study is potentially subject to a number of sources of bias, such as inaccurate definition of exposure variables and the confounding factors of unmeasured variables (length of residence, occupation, cigarette smoking, alcohol drinking, etc.), leading to a reduction of the estimation of possible risk. They conclude that further studies based on individuals should be carried out in which more direct control of potentially confounding factors will be possible. Until such studies are carried out, the implications of the present findings for the population located near PICs must remain uncertain. Therefore, this county-based study may provide leads to more detailed investigation, but conclusions based on this kind of study must of necessity be tentative.

Source: Journal of Toxicology and Environmental Health, 50, Feb. 1997.

New Technology for a Universal Blood Type

In human blood transfusion, if blood of type A or B is given to someone with type O blood, the ensuing severe immune reaction can rapidly kill the person. Type O blood, however, can be given to anyone; and type A blood presents no problems for someone who happens to be A or AB. The danger arises when, for example, a type O patient gets A or B blood, or when a type A patient gets B blood. Unfamiliar molecules on the surface of the foreign blood cells trigger the immune system causing a state of shock in the patient with rapid kidney failure and depletion of blood-clotting factors resulting in death.

Some hospitals try to lessen the chance of a fatal mistake by stocking only type O blood for emergency rooms and intensive care units, where blood-handling accidents are most likely to happen.

However, this practice can create a shortage of type O blood and may mean that A and B blood goes to waste because hospitals cannot use those units within their 42-day shelf life.

The Role of Copper in Oral Cancer

In many Asia and Pacific Rim countries it has long been known that oral cancer is associated with chewing betel nut, a once widespread habit in the area. It is a particularly virulent form of the disease, and survival rates for patients diagnosed with it are poor.

In the past, it has not been clearly understood why betel nuts should cause cancer. However, a group of researchers studying oral cancer under a World Health Organization programme has found high copper levels associated with betel nut, both in aqueous extracts prepared in the laboratory and in saliva from volunteers who have chewed it. The group was alerted to this possible link by past studies which have shown that high copper levels are often associated with fibrotic diseases.

In their study, they prepared extracts from commercially available betel nuts in water, after which they measured copper concentrations using atomic absorption spectroscopy. These experiments showed that copper levels were very much higher than those from peanuts, that are commonly eaten as a snack.

Copper was measured in saliva from three adult volunteers before and after chewing betel nut. Baseline levels of copper were established by measuring saliva collected early in the morning. After the volunteer had chewed betel nut, the researchers sampled their saliva at ten minute intervals for one hour. Atomic absorption measurements showed that copper concentrations rose from an average of $18gl^{-1}$ before chewing to $122\ gl^{-1}$ as the betel nut was chewed. The copper then took 40 minutes to return to its normal concentration.

As a result of this study, the researchers suspect that copper is the active ingredient in the occurrence of oral cancer in chewers of betel nut. They have speculated that it induces activity in the enzyme lysyl oxidase, which in turn stimulates the activity of the fibroblast cells and leads to crosslinking of the collagen of the oral tissue. However, the exact reason why these biochemical changes lead to full development of fibrosis and oral cancer in some patients remains to be discovered.

Source: Chemistry in Britain, Vol. 33, No. 6, June 1997.

Now, however, researchers claim to have found a solution to this problem by chemically changing types A and B red blood cells into the universal type O. This has been achieved by using an enzyme to alter the chemistry of the red cell surface. Chains of sugars, which cover the cell surfaces of the four human blood types (A, B, AB and O), all have the same basic sequence, with fucose at the end of the chain and galactose next in line. The major distinction between blood types lies with the sugar that branches off from the galactose.

O cells have no additional sugar at all, while AB blood cells bear a mix of A and B chains. In the United States, about 45 percent of the population has type O blood, 40 percent has type A, 11 percent has type B, and 4 percent has type AB.

A and B cells cannot be transfused into people with O blood because the extra sugar branch stimulates the immune system's antibodies to attack the foreign cells. Clipping off that additional sugar branch from A and B cells transforms them into type O, averting the immune response.

The enzymes for A and B conversion have now been identified, and once conversion technology for A and B blood is established, altering the AB cells should be straightforward. However, any technology that would convert blood to a true universal donor type must take another characteristic, Rh factor, into account. A cell surface protein first discovered in the blood of Rhesus monkey, the Rh factor can provoke an immune reaction in people whose blood doesn't normally carry it. People who have the protein on their red blood cells are deemed Rh-positive; those who don't are Rh-negative.

Researchers are only beginning to explore techniques for Rh conversion. If researchers can identify which part of the protein stimulates the immune response, then perhaps they can alter that portion to make the blood cell effectively Rh-negative. Eventually they want to produce type O, Rh-negative blood – the kind any person can receive without fear.

Source: Science News, Vol. 151, No. 2, January 11, 1997.

Occupational Asthma

According to a recent report in the Lancet, as many as one in five cases of asthma may be due to exposure to chemicals in the workplace. Occupational asthma is a potentially fatal condition. Some 250 chemicals have been found to cause occupational asthma. Grain dust has been found to cause asthma in grain-store workers; henna in hairdressers; coffee beans in coffee-roasters; flour in bakers; penicillin in pharmacists and health-care workers; cobalt dust in metal grinders; and oil mists in tool setters.

In some cases, occupational asthma is caused by an allergic immune reaction to a specific substance, but irritating chemicals, gases, and fumes can act directly on and damage bronchi, triggering what is called irritant-induced asthma.

Occupational asthma usually appears soon after a worker is first exposed to the asthma-inducing chemical, but sometimes it may appear months to years later. The total duration of exposure, the duration of symptoms, and the severity of asthma at the time of diagnosis are important determinants of outcome.

Early diagnosis and early withdrawal from exposure are the keys to complete recovery.

News item.

Biomarkers in Tea and Cancer Research

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biomarkers which are both non-invasive and provide meaningful data with respect to cancer risk. Hydroxylated DNA bases in urine are good markers of oxidative DNA damage, and raised levels of this lesion have been found to correlate significantly with cancer in animal tissues. In readily accessible human cells, an increase in chromosome abnormalities has been linked to cancer. However, increasing attention is being paid to the micronucleus frequency assay, which can be used to measure whole chromosome loss and strand breaks as well as excision repair events arising from DNA adduction. Strategic use of appropriate biomarkers should contribute to a meaningful evaluation of the possible role of tea polyphenols in protection against carcinogenesis at various levels and should also help to identify the stages in the development of cancer at which tea may be most effective.

Source: Cancer Letters 114, 1997.

Biomarkers in Environmental Applications

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Aromatics.

Biomarkers of effect, and more biomarkers of susceptibility should be developed for aromatics.

1, 3-Butadiene.

The exposure of workers in representative workplaces must be characterized to determine whether current levels of butadiene exposure produce significant responses in exposure or effect biomarkers.

Also it should be determined whether subsets of individuals exist with unusual susceptibilities to the toxic effects of butadiene.

Polycyclic Aromatic Hydrocarbons.

Integrated studies involving a variety of health professionals should be conducted. Field and laboratory studies should be undertaken not only to understand the exposure in the population, but also the interaction between markers of exposure, effect, and susceptibility (e.g., PAH-metabolites, PAH-hemoglobin and DNA adducts, mutation, P4501A1, and glutathione S-transferase). The study of markers of susceptibility should not be a top priority until the interrelationships of exposure and the markers are established.

Metals.

Chromium-induced protein-DNA cross-links and association with disease (not gene specific) must be validated.

Other biomarkers of effect for manganese should be sought and the mechanism of action in toxicity should be defined as should non-genetic factors of susceptibility.

Source: Adapted from Environmental Health Perspectives, Vol. 104, Supplement 5, October 1996.

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