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"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

Insecticide Applications of Neem Tree Extracts

Extracts obtained from the seeds or seed kernals of the neem tree have been found to possess insecticidal properties. The principal active ingredient is the limonoid, azadirachtin.

Azadirachtin is particularly effective against lepidopteran larvae, and exhibits both growth-regulating and antifeedant effects. Thus, neem-based insecticides are being investigated as potential alternative control agents for forest insect pest management.

Recent research by the Canadian Forest Service has indicated that neem-based insecticides are quite effective in controlling several forest insect pests and these extracts are likely to become increasingly important in the development of integrated forest pest management strategies. The basic principles of integrated forest pest management programs are largely driven by environmental concerns; thus it is important that the development of such strategies should be accompanied by appropriate environmental safety testing.

Experiments carried out by the Canadian Forest Service indicated that there is little risk of direct adverse effects on aquatic macroinvertebrates resulting from contamination of water bodies with neem-based insecticides used in forest pest management applications. This finding is of particular importance in Canada where much of the forested land contains large numbers of water bodies and there was concern that the use of forest insecticides might result in contamination of water courses.

The conclusions of the recent study are based on the following data:

(1) Flow-through screening tests indicated that short-term exposures to concentrations as high as 10 times the maximum expected environmental concentration (EEC) did not cause lethal effects in seven of eight test species.

(2) Concentration-dependent tests with *Isonychia bicolor/rufa* demonstrated a wide margin of safety (LC_{10} of 18 times the EEC) for lethal effects on these species of mayflies.

(3) The microcosm experiments demonstrated that even at longer-term exposures to the EEC of 0.035 mg/liter, azadirachtin did not express antifeedant activity or mortality in three species of detritivorous invertebrates. The arrays of species tested in these systems represents a reasonable cross-section of the aquatic macroinvertebrates likely to be encountered in forest water bodies.

Source: Ecotoxicology and Environmental Safety, February 1997.

Effects of Cadmium on Bone

Cadmium exposure induces bone resorption *in vitro* and *in vivo* that can lead to low bone mass and increased incidence of fracture. The mechanism of cadmium's actions on bone cells is unclear, although effects on cell to cell communication via cytokines or other messengers responsible for normal bone remodeling have been postulated.

Most *in vivo* cadmium exposure models measure the response to chronic cadmium exposure, or measure the bone response in time periods ranging from weeks to months. While many of these studies provide insight into the action of cadmium *in vivo*, few models have been designed to study the cellular and molecular mechanisms of cadmium exposure.

Researchers at the Center for Mechanistic Biology and Biotechnology at the Argonne National Laboratory, Illinois, U.S.A., have now developed an animal model for following early skeletal response to cadmium. It uses a single gavage dose of cadmium and does not require the use of calcium for verification of the skeletal response. It is based on experiments using mice with skeletons prelabeled with calcium where increased fecal excretion of the substance was not the direct result of calcium release from bone.

The model also uses a low-calcium (but not calcium-deficient) diet to increase gastrointestinal absorption of calcium, so that the endogenous fecal calcium excretion is equal to the total fecal calcium excretion, with essentially no contribution from dietary calcium. In essence, the cadmium-induced bone response can be determined by quantitating stable fecal calcium.

Results obtained from the study suggest that a threshold level of cadmium is required for a bone response but that chronic levels of cadmium in blood do not necessarily indicate the occurrence of continuous active bone resorption.

This model can be used to investigate the early bone response to cadmium with respect to cadmium-induced bone cell gene expression and nongenomic mechanisms.

Source: Toxicology and Applied Pharmacology, Vol. 145, 1997.

EFFECTS OF EXPOSURE TO MERCURY FROM DENTAL AMALGAM FILLINGS

Studies on both humans and animals have shown high levels of mercury in oral mucosa after exposure to dental amalgam fillings. The toxicological consequences of this exposure are a subject of debate in several countries, and in some European countries the health authorities recommend that individuals in risk groups such as pregnant women and individuals with kidney disease should avoid treatment with dental amalgam.

However, the influence of dental amalgam fillings on mercury concentrations in saliva and feces is not known in detail and the interpretation of mercury concentrations in these media is unclear. Possibly, a part of the mercury retained in the oral mucosa, gingiva, and gastrointestinal tract will influence mercury levels in both saliva and feces.

In order to elucidate the effects of this influence, a study has been carried out in Sweden to present data on mercury concentrations in saliva and feces of individuals with and without amalgam fillings. The study has also investigated mercury concentrations in saliva, feces, urine, blood, and plasma, after exposure to mercury in conjunction with removal of amalgam fillings.

Ten subjects ("amalgam group"; three men and seven women) with a mean age of 38 years (SD 7.5, range 27 to 52) and a mean number of 19 amalgam surfaces (SD 6, range 13 to 34) had all amalgam fillings removed at one dental session (Day 0). Water-spray cooling and a high volume evacuator were used during the removal. A reference group consisted of 10 subjects (three men and seven women) with a mean age of 20 years (SD 1.4, range 18 to 23) who had no history of dental amalgam fillings. The subjects refrained from intake of all kinds of fish from 1 month before the start of the study to the end of the sampling period. Mixed saliva was collected in plastic tubes in the morning before breakfast and brushing the teeth. The plastic tubes were checked for mercury contamination and no detectable mercury was found. Fecal samples were collected in plastic bags and polyethylene jars. After collection, the fecal samples were homogenized and stored frozen at -20°C. Samples of saliva and feces were collected on six different occasions: two baseline samples were collected the week before amalgam removal (Days –7 and –2) and additional samples were collected 2, 7, 14,

CADMIUM LEVELS IN GRAZING LAND

Research carried out in the United Kingdom reports abnormally high levels of the toxic metal cadmium accumulate in the kidneys and livers of sheep grazing on pasture fertilized with sewage sludge.

Scientists measured levels of heavy metals accumulated by sheep when they grazed on one field that was treated with sewage sludge and on another field that was untreated. After five months, average levels of cadmium in sheep livers were 1.24 milligrams per kilogram of dried tissue for the animals that had grazed on sludge treated pasture. This was eight times higher than the level found in sheep grazing on untreated land.

In sheep kidneys, the levels in animals that had grazed on the sludge treated land averaged 2.57 milligrams per kilogram of dried tissue, which was six times greater than the sheep that grazed on untreated pasture.

The sludge remaining after sewage treatment is sometimes rich in cadmium because sewage contains residues of the metal from industrial processes such as electroplating. It is uncertain, however, whether the levels of cadmium reported in the research study would be dangerous to human health if the animal offal were regularly consumed.

The researchers point out that their study represents a "worst case scenario" in that the pasture in question had received sludge regularly between 1981 and 1995. The average concentration of cadmium to a depth of 25 centimeters below the surface was 2.72 milligrams per kilogram of dried soil, close to the legal limit of 3 milligrams. Nearer the surface, in soil likely to be eaten with grass by grazing sheep, the concentration was 4.97 milligrams per kilogram of dried soil.

These finding pose a problem to European agriculture if the practice of spreading sewage sludge on pasture land intensifies as is likely in Europe after 1998 when dumping of sludge at sea will be banned.

Source: New Scientist, March 22 1997.

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and 60 days after amalgam removal. From the amalgam group samples of blood were collected in heparinized glass tubes the week before amalgam removal and at 3, 7, 24, and 31 hr. and 2, 3, 4, 7, 14, 21, 30, and 60 days after amalgam removal. Urine samples (24-hr. collections) were collected in acid-washed polyethylene vials during the days of the blood sampling.

The results of the study revealed that, after amalgam removal, a minor transient increase of the median mercury concentration in plasma was found with a maximum 2 days after the removal. In blood, however, there was no significant increase in mercury concentration. Sixty days after removal, mercury concentrations in both blood and plasma had declined significantly. The median concentration of mercury in saliva also decreased significantly after amalgam removal. In the amalgam-free reference group, the median value was three orders of magnitude lower than the amalgam group. However, sixty days after amalgam removal there was no significant difference between the groups. The median mercury concentration in feces was more than ten times higher than the reference group median. After a considerable increase 2 days after amalgam removal, to a median of 280 µmol Hg/kg dry weight, there was a significant decrease of mercury in the feces in the amalgam group after one week, when the median value was 7.5 µmol Hg/kg dry weight. Sixty days after amalgam removal, the mercury concentration was, however, still slightly higher than the median value of the reference group.

At several time points, significant associations between mercury levels in saliva, plasma, feces, and number of amalgam fillings were found, emphasizing the importance of dental amalgam as a source for mercury in these media. Interestingly, even 60 days after amalgam removal there was a significant association between mercury in saliva and plasma and the subject's number of amalgam fillings before removal. This further supports the hypothesis that part of the mercury in these media has a long biological half-life. In addition, mercury exposure from sources other than amalgam during the study period must have been very low. The association between mercury in saliva and feces may be a result of the limited uptake of salivary mercury from the gastrointestinal tract. Furthermore, the significant correlations may be explained by an association between plasma mercury and a fraction of the body burden of mercury which, in turn, could be reflected by mercury concentration in feces and saliva long after amalgam removal.

Amalgam fillings are a significant source of mercury in both blood and urine as well as saliva and feces, and mercury levels in all media decrease after amalgam removal. The findings from this study support the hypothesis that oral mucosa is a reservoir for mercury released from dental amalgam. Possibly, the mercury concentration in mixed saliva could be an indicator of the mercury concentration in oral mucosa, and additional studies are needed to further investigate this possibility. Fecal excretion of mercury is strongly influenced by amalgam fillings, especially in conjunction with their removal. Hence, data on fecal excretion of total mercury are not a valuable indicator of the systemic exposure to mercury from amalgam fillings.

Source: Toxicology and Applied Pharmacology, May 1997.

BIOREMEDIATION OF MARINE OIL SPILLS – A CHALLENGE FOR BIOTECHNOLOGY

Most crude oils are inherently biodegradable, with estimates ranging from 70-90% for different types of oil. One option for stimulating biodegradation of oil slicks that result from accidents to container vessels at sea is to accelerate the natural process of biodegradation by adding chemical dispersants to the area of the slicks. The use of dispersants is believed to stimulate the natural process of biodegradation because microbes can attack the slick at the oil-water interface and dispersion of the oil dramatically increases the area available for microbial colonization. Dispersal also facilitates the action of other nutrients, such as nitrogen, required for the growth of bacteria.

Bioremediation played a major role in the clean-up operation after the Exxon Valdez oil spill in Alaska in 1989. Although crude oils are inherently biodegradable, they do not contain the nitrogen, phosphorus or trace elements essential for microbial growth. In treating this spill, bioremediation focused on partially alleviating the nutrient limitation by the addition of fertilizers to the area of the slick. This approach was found to be highly successful, accelerating the natural rate of biodegradation by up to five times with no detectable adverse environmental impacts.

Biotechnology presents yet other approaches to dealing with oil slicks by improving the degrading abilities of bacteria that could be applied to oil spills by means of genetic engineering. To date, however, little progress has been made in developing robust strains of organisms for this purpose. There are, moreover, concerns that if such strains were developed they might have an adverse impact on the shoreline environment.

Current research, therefore, aims at gaining a better understanding of the shoreline environment where biodegradation occurs in order to discover ways of stimulating the indigenous microorganisms without adverse environmental impacts. Researchers are optimistic that if we are able to understand the fundamental microbial ecology of a spill site we shall be able to develop more effective approaches to clean-up operations.

Source: Trends in Biotechnology, May 1997.

Transient Impact of Pesticides on Aquatic Organisms

Most rivers in Japan have rice paddies on both sides. These fields are sprayed with many kinds of pesticides during the rice planting and growing season. Young rice seedlings are transplanted from the rice nursery to paddy fields which have been cultivated after introduction of river water. Therefore, most rivers in Japan tend to suffer pesticide contamination, although the concentrations are generally low and transient.

A recent study investigated the correlation between overall pesticide effects monitored by shrimp mortality and change in macrobenthic fauna in the Suna River which flows through the rural district of Yamagata Prefecture in northeastern Japan about 500 km north of metropolitan Tokyo. This river was selected for the study because pesticide application had been restricted for a long time in the upper reaches, while aerial insecticide spraying had been carried out four times on paddy fields in the lower reaches in summer.

It was considered that the shrimp mortality in the river water samples collected in the study was entirely caused by pesticide toxicity, mainly attributable to the various insecticides sprayed on the paddy fields. Interestingly, the shrimp mortality which lasted during the insecticide spraying period suddenly disappeared after the last insecticide spraying. This suggests that no other toxic chemicals existed in the Suna River, at least during the time of the study.

Source: Ecology and Environmental Safety, February 1997.

CORAL BLEACHING AS A BIOMARKER OF ENVIRONMENTAL STRESS

Coral bleaching occurs when host corals lose symbiotic algae living within their tissues or when these algae themselves lose pigmentation. While some bleaching events are reversible and do not kill corals, extensive bleaching can cause large rates of coral mortality and local extinctions. There is evidence that coral bleaching events may have increased dramatically in the last twenty years, and since coral reefs play a significant role in the economies of many tropical islands and countries, bleaching has the potential to have devastating economic as well as ecological effects in these areas.

Reef fishing communities have been shown to be significantly affected by changes in live coral cover, with some species of fish disappearing from dead reefs. Even small changes in live coral cover have produced significant changes in the total number of species present. In addition to losing coral polyps as a source of food, resident fish species and other organisms lose living spaces associated with the structural complexity of live corals.

Preliminary studies demonstrate high variability in coral reef recovery rates following mass bleaching events. Areas that suffered 50-70% coral mortality following the 1982-1983 El Niño Southern Oscillation event in the eastern Pacific showed erratic and slow recruitment of new corals after a period of ten years. On the other hand, colonies of *Montastrea annularis,* which suffered 90% bleaching in some parts of the Florida Keys during the 1987 mass bleaching event, were still alive in 1989.

Several researchers have documented coral recovery after bleaching episodes, with results varying from partial recovery to severe degradation. From these studies it is apparent that reef recovery will depend on many factors, such as the initial severity of bleaching, persistence of initial stressors, existence of other stressors that may further degrade weakened corals, density of healthy corals that can produce planulae after bleaching, and availability of suitable substrate on which planulae may settle. However, it is clear that bleaching has the potential to severely degrade reef systems over long periods of time, and is therefore a threat to economies that depend on healthy reef systems.

As a biomarker of environmental stress in tropical ecosystems, coral bleaching has the advantage of being easily observable. Bleaching, moreover, appears to be a generalized response caused by many different stressors or combinations of stressors. Thus, it is a useful indicator of a wide variety of coral insults, which inherently takes into account synergistic or additive qualities of stressors.

While detecting bleaching events is not difficult, determining their etiology remains a challenge. To date, few studies have been completed that detail events occurring at the molecular, subcellular, and cellular level in coral and zooxanthellae tissues subjected to bleaching. The detailed understanding of this complex global problem, necessary to identify a possible remedy, will be accelerated as toxicologists begin to address these issues.

Source: Journal of Toxicology and Environmental Health, April 1997.

NATURAL PLANT DEGRADATION OF OZONE DEPLETERS

Scientists from the US Environmental Protection Agency have reported that leaves from nine different species of plant will reactively remove a number of halogenated hydrocarbons from air. The compounds are hexachloroethane (HCA), tetrabromoethylene (TBE), ethyl bromide (EBr) and methyl bromide (MeBr). The leaves of plants as varied as sorrel, swamp iris, chrysanthemum, a weed variety of poppy, and trees such as dogwood and maple absorb HCA and TBE very rapidly, while MeBr disappears with a half-life measured in hours. (In contrast, no removal of carbon tetrachloride has been observed). The rate of removal varies with leaf area, and the rates differ from plant to plant by a factor of 20.

The active agents of removal appear to be enzymes acting within the leaves, and these enzymes are robust enough to survive the death and decay of plant, remaining active in the anaerobic soils found in wetlands. This would explain the ability of pond sediments and aquatic algae to degrade contaminants ranging from TNT to halogenated hydrocarbons.

An important finding reported by EPA scientists is that the rapid and almost complete removal of HCA within two hours is followed by production of gaseous tetrachloroethylene (TCE) over the next two days. However, TCE accounts for only 10 per cent of the missing HCA, and it has not yet been established whether this is because TCE undergoes further degradation, or whether it is absorbed by the plants. It seems most likely that it is degraded further since that is what has been observed with tetrabromoethylene (TBE), which is converted to gaseous tribromoethylene. These findings raise questions with regard to the banning of MeBr as an ozone depleter.

Source: Chemistry in Britain, June 1997.

LIVER DAMAGE LINKED TO CFC SUBSTITUTE

A Belgian occupational health physician, puzzled by several cases of acute hepatitis at a smelting plant, contacted the Industrial Toxicology and Occupational Medicine Unit of the Catholic University of Louvain, for advice.

Researchers found nine men with liver damage, all drivers of an overhead gantry in the smelting plant. The refrigerant used in the air-conditioning system that cooled the cabin had been changed prior to the onset of the health problem from CFC-114 to a mixture of HCFC-123 and HCFC-124. It was found that holes in the plastic piping had been leaking HCFCs into the cabin. No new cases of hepatitis or recurrences have occurred at the plant since the system was fixed.

A matter of considerable concern to industrial health experts is that the U.S. Environmental Protection Agency (EPA) considers HCFC-123 to be an extremely important substitute for ozone-depleting CFCs, and it is considered very safe when used correctly.

EPA also has approved HCFC-123 for use in fire suppression, solvent, and foam-blowing applications.

Source: Chemical & Engineering News, August 25, 1997.

THE EFFECTS OF NITRATES IN OUR DIET

Researchers form the University of Aberdeen in Scotland are taking a fresh look at the effects of nitrate compounds in our diet. Since the 1970s, nitrate has been held to be a dietary evil. Nitrate-contaminated well water has been linked to rare cases of oxygen starvation in babies, while nitrosamines, the nitrate compounds formed during the digestion of some meat products, has been implicated as a cause of stomach cancer. However, more recent research indicates that moderate amounts of nitrates are not dangerous to adults, and indeed might have a useful role in our diet by protecting us against such potentially fatal bacteria as *Salmonella, Shigella,* and *Escherichia coli.* Most dietary nitrates come from green-leaved vegetables and some studies have shown that vegetarians have lower than average death rates from cancer.

While some scientists believe it is time to reassess the effects of nitrates on our health, they in no way dismiss the hazards posed by water contamination by high levels of nitrate fertilizers. They would like, however, to change the perception that nitrates in vegetables are bad.

News Items.

New Cancer-fighting Agents

At a meeting of the American Chemical Society held in Las Vegas in September, researchers from Purdue University, Indiana, reported on their work which has led to the identification of more than forty compounds with potential anti-cancer properties from the bark of the North American pawpaw tree.

This research has revealed that compounds derived from pawpaw show potential in fighting certain types of cancer that have proven resistant to other drugs.

Bullatacin, one of the compounds identified, was found to be able to inhibit the energy required by drug-resistant cancer cells in purging anti-cancer agents, and to eventually kill the resistant cells.

The effect of bullatacin on drug-resistant cells has been studied only in laboratory cultures and will now require additional study in animals before it can be tested in humans.

News Items.

EFFECT OF SOLVENT EXPOSURE ON THE NERVOUS SYSTEM

All types of organic solvents are volatile liquids at room temperature and are lipophilic. Because of the large number of solvents and their increasing use in new technologies, there are many occupations in which workers can be exposed to them.

The main routes of exposure are through inhalation and skin contact. After absorption, solvents may be exhaled unchanged, biotransformed and then excreted, or accumulated in lipid-rich tissues such as the brain, myelin, and adipose.

The toxicity of particular solvents to human beings depends on the mechanism of action and the amount or dose of exposure. When solvents are used as mixtures, or contain impurities, the effects may be additive, synergistic, or portentiated.

Solvent-induced nervous-system dysfunction is diagnosed when the symptoms, signs, and evidence from laboratory studies are typical of those seen in solvent intoxication, when a solvent exposure can be confirmed, and when there is no other medical or historical explanation for the examination results.

Differential diagnosis of CNS dysfunction secondary to solvent exposure can be tricky. Examples of neurological disorders with overlapping symptoms and laboratory findings to those seen in solvent toxicity include multiple sclerosis and cerebrovascular dementia (both of which affect the white matter and cognition). Differential diagnosis relies on history, progression, and the use of other laboratory tests and clinical findings.

Some patients with solvent exposures develop psychological disorders in which cognitive changes can be seen (these include post-traumatic stress disorder, depressive disorders, and motivational disorders such as malingering or sick-role playing) or have developmental disorders in learning or attention that affect cognitive test results.

In these cases, the patterns of neuropsychological test performance and history are high, specific and informative. Many patients with histories of exposure to solvents complain of symptoms that fit diagnostic criteria for chronic fatigue syndrome or for multiple chemical sensitivity. In these disorders, cognitive test results generally differ from those found in solvent-exposed patients and the characteristic signs, symptoms, and laboratory findings of solvent intoxication are absent.

Another issue important in differential diagnosis is the synergistic interaction between exposure to industrial solvents and ethanol, which can result in a more pronounced picture of nervous-system effects in an alcoholic than in a patient who abstains from alcohol use.

Treatment options in patients with toxicant-induced neurological disorders are limited. The first step is usually to remove the patient from exposure until symptoms remit, and to judge carefully whether it is advisable for the affected individual to work with solvents in the future. Such decisions may require follow-up assessments of neurological and neuropsychological status to assess recovery and residual impairments.

Source: The Lancet, April 26, 1997.

A FATALITY FROM ONE ACUTE EXPOSURE TO DIMETHYLMERCURY

The death of a highly esteemed researcher as the result of a laboratory accident involving exposure to dimethylmercury has prompted her colleagues from Dartmouth College U.S. to warn the chemistry community that disposable latex and PVC gloves do not offer sufficient protection against certain hazardous materials. The researcher was using nuclear magnetic resonance (NMR) spectroscopy to investigate the binding of mercury ions to a protein involved in DNA repair. The resonance of each element studied in NMR spectroscopy is measured in reference to a standard compound that contains that element. In this instance, the researcher chose dimethylmercury as a standard for the mercury measurements.

The researcher spilled a small amount of the colorless liquid compound on her latex gloves while transferring it to an NMR tube and, although she was most likely unaware of it at the time, the toxic material apparently permeated the gloves and seeped into the researcher's skin in a matter of seconds. She became ill a few months later and died of mercury poisoning less than one year after the single exposure. Although currently only a small number of laboratories utilize mercury NMR, it is likely that the number will grow in the next few years because the approach provides a powerful tool for investigating biological systems.

Because mercury can be substituted for metals such as zinc and copper, which do not give NMR signals, mercury NMR can be used to examine the metal-ion binding sites of proteins crucial to biological processes.

As a result of the tragic accident that occurred in August 1996, the chemical's distributors have updated the safety information that is sent to those who purchase dimethylmercury.

Source: Scientific American, September 1997.

CADMIUM TRANSFER TO EGGS OF LAYING HENS

A study carried out by researchers from Hokkaido University, Japan, has measured the transfer of cadmium from laying hens to eggs, and the possible effect of cadmium exposure on hatching ability. Cadmium is a toxic environmental contaminant known to accumulate mainly in the livers and kidneys of human beings and various experimental animals.

In comparison with mammals, cadmium accumulation in the liver and kidney has been reported in white Leghorn laying hens, Japanese quail, and turtle doves after oral administration of cadmium. Previous reports have described low amounts of cadmium accumulation in eggs. However, past studies have not determined whether cadmium would accumulate in the yolks when maternal animals are exposed to high amounts of the subtance.

However, the Japanese study using thirty-eight twelve-month-old white Leghorn laying hens demonstrated that transfer of cadmium from cadmium-injected laying hens to the eggs was restricted even when high amounts of cadmium accumulated in maternal liver. In this study, eggs accumulated low concentration of cadmium even when 140 µg/g wet tissue of the substance had accumulated in the maternal livers. The findings suggest the presence of a protective mechanism restricting the transfer of cadmium between maternal birds and their eggs.

Source: Journal of Toxicology and Environmental Health, May 1997.

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