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INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

CRI's ICEIT has been designated as a
"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

CRI Organizes Executive Seminar and Training Course on Environmental Toxicology

HRH Princess Chulabhorn, President of the Chulabhorn Research Institute, opened the Executive Seminar on Environmental Toxicology on 16 August 1999 at the Shangri-La Hotel in Bangkok.

The program of the seminar and the training course was designed on the basis of CRI's experience over the last 12 years since HRH Princess Chulabhorn initiated the international training program in Environmental and Industrial Toxicology at CRI.

The experience of organizing training courses and workshops for developing countries, primarily in the Asia Pacific region, has provided the Institute with a clear perception of the training needs in environmental toxicology to develop human resources to address regional priorities with a special focus on local conditions and practices, thus providing a sound basis for sustainable industrial development.

In her opening address at the Executive Seminar, HRH Princess Chulabhorn stated that the rapid industrial expansion that has taken place in the region in recent years has led both government agencies and the industrial sector to examine more critically the effect of such development on the natural environment and on human health.

The significance of the seminar and the two week training course that followed was the special emphasis on sustainable industrial development within the context of national development as a whole, involving the cooperation of all sectors. This was reflected in the selection of participants for the seminar and workshop to ensure that all sectors were well represented. The participants came from 12 countries in Asia and the Pacific.

Health Effects of Food Contamination by PCBs and Dioxins

When a poisoning episode broke out in a number of poultry farms in Belgium in February 1999, the authorities took immediate safeguards to protect public health.

The first symptom of contamination was a sudden drop in egg production. A few weeks later, there was a marked reduction in egg hatchability, along with reduced weight gain and increased mortality of chicks. These birds presented with ascites, subcutaneous oedema of the neck and neurological disturbances (ataxia). Histology revealed degenerative changes of the skeletal and cardiac muscles. The lesions resembled "chickoedema disease", which was reported during the 1950s to 1970s in several outbreaks of poultry poisoned by polychlorinated biphenyls (PCBs) and dioxins, suggesting that dioxins might be responsible for the Belgian cases. High concentrations of dioxins in chicken meat and feedstuff were subsequently found and, at the end of April, the source of dioxins was traced to a stock of recycled fat that had been delivered to a manufacturer of animal feed in mid-January.

Analysis of contaminated feedstuff and poultry products showed a consistent pattern of dioxin congeners, dominated by the polychlorodibenzofurans (PCDFs). Polychlorodibenzodioxins (PCDDs), in particular the 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin involved in the 1976 Seveso accident in Italy and in contamination by the Agent Orange defoliant, were present only in minor proportions (less than 5%) of total congeners. This pattern of PCDD and PCDF congeners was virtually identical to that in the contaminated rice oil that poisoned 2,000 people in 1968 in Yusho, Japan.

All contaminated samples contained increased amounts of PCBs, which closely correlated with the concentrations of PCDDs and PCDFs, having an average ratio of PCB:PCDD/F of about 50,000:1. The PCB pattern in feedstuff was closely matched to a PCB mixture composed mainly of Aroclor 1260. In contaminated poultry meat and eggs, the distribution of PCB congeners was altered because of the preferential biological transformation and clearance of the lower chlorinated congeners (PCB 52 and 101).

The outbreak of dioxin contamination in Belgium is an almost exact replica of the outbreaks of poultry poisoning by polychlorinated compounds that occurred repeatedly in the United States and Japan in the 1950s to 1970s. These outbreaks produced the same effects on the avian reproductive system as the Belgian contamination. Two of these previous reports also involved PCB mixtures (Kanechlor 400 and Aroclor 1242).

As in earlier accidents, it is very unlikely that the isolated episode of contamination in Belgium will cause adverse health effects on the general population. It would require the consumption of 30-40 meals of highly contaminated chicken or eggs (dioxin levels of around 1,000 pg Toxic Equivalents per g fat) to double the body's PCB and dioxin burden. Even in such an extreme case, the maximum body burden would still be at least a factor of one hundred less than in the victims of the Yusho accident and in the Seveso residents (referring to the mean value in the most contaminated zone), but would be similar to the two to threefold increase in PCB and dioxin body burden of subjects affected in the 1980s or of those regularly eating contaminated seafood.

Source: Nature, Vol. 401, September 1999.

Mass Poisonings with PCB Mixtures

Mass poisonings with PCB-containing mixtures have occurred twice – once in Taiwan and once in Japan. In each instance contaminated rice oil was the source. The contaminating mixture contained PCBs, PCDFs, and other related compounds. The toxic effects of the mixture could be due to dioxin-like activity, with PCDFs the major contributor, or to effects mediated by other mechanisms of potential importance, as the mixture contained primarily PCBs. Studies of the health effects in these incidents are informative about high-dose adult and *in utero* exposures to the mixtures. Much of the available data on health effects are from case series and may reflect findings in the most severely affected. The standardized mortality ratio for the studied, exposed adult populations in Taiwan (n~1900) and Japan (n~1800) 10 and 20 years after the incident, respectively, was 1.1 in both populations. Deaths from non-malignant liver disease were increased in both populations. In Japan an excess of deaths from liver cancer was evident. In both populations, the exposed subjects had increased prevalence of chloracne, localized hyperpigmentation, abnormalities of the dermal tissues adjacent to the eye, slowed nerve conduction, abnormalities of a number of laboratory tests on blood, and other symptoms. A group of exposed subjects from Japan had elevated T_3 and T_4 levels 16 years later.

The Taiwanese children exposed to the mixture *in utero* were systematically followed and studied. Within 4 years of birth, 21% had died. The children had many of the same manifestations of toxicity as the adults, and in addition had delayed, inhibited growth, permanent intellectual impairment, disordered behavior, more frequent infections, and other problems. Several of the symptoms in human infants resemble the developmental effects observed in experimental animals exposed *in utero* to PCBs. It is not known if the reproductive, cognitive, and psychomotor effects and the hearing difficulties have been linked with possible endocrine disruptive effects of PCBs in the Yu-cheng and Yusho infants.

Given the complex nature of mixtures of PCBs that human individuals are exposed to and the dependency of toxic outcome to the congener composition of mixtures, it is essential to design and distribute environmentally relevant reconstituted PCB mixtures to improve comparability of studies and consistency of results.

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DIOXIN CONSIDERED A HUMAN CARCINOGEN: THE WEIGHT OF THE EVIDENCE

Human studies of the carcinogenic effect of dioxin conducted over the last twenty years have raised suspicions about dioxin exposure and risk of cancer. However, for most studies there has been no documentation that the cohorts investigated in epidemiological investigations were actually exposed to high levels of dioxins.

However, a comprehensive review conducted by the International Agency For Research on Cancer (IARC) in 1997 focused on four industrial cohorts with well-established exposures to 2, 3,7,8-tetrachloro-dibenzo-p-dioxin or TCDD.

This review yielded a remarkably consistent result of about a 40% overall increase in cancer mortality that was highly statistically significant.

The IARC working group that carried out the review commented that the strong evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites, appears to be unique compared to established human carcinogens.

The sum of the available evidence, thus, points to dioxin being a human carcinogen. Specifically, the consistent impact of high-level TCDD on total cancer mortality, along with animal testing results and mechanistic considerations that would make such an effect plausible, should lead to acceptance of the association unless proven otherwise.

Source: Journal of the National Cancer Institute Vol. 91, No. 9, May 1999.

CONCERN OVER DIOXIN LEVELS IN JAPAN

The Japanese government is taking steps to reduce the high concentrations of dioxin in the environment. Earlier this year the first ministerial conference on dioxin policy in Japan reviewed maximum tolerable daily intakes. The problem of dioxin emissions is particularly serious in Japan since 75% of all waste is incinerated. Approximately 90% of the country's emissions of dioxin are reported to come from waste incinerators and the burning of chlorine-based chemicals. It is expected that the government review will lead to national debate on the issue and that one outcome of the current level of concern will be the promotion of recycling programs as a means of reducing the level of waste incineration. Further ministerial conferences will be held to discuss dioxin concentrations in soil and food.

Source: British Medical Journal Vol. 318 March 1999.

The association of dioxin exposure with non-Hodgkin's lymphoma

The International Agency for Research of Cancer (IARC) recently convened a working group to evaluate evidence concerning the carcinogenicity of 2,3,7,8-Telrachlorodibenzo-p-dioxin (TCDD). In 1997 after evaluating epidemiological studies and the results of animal experiments, the working group classified the compound as a human carcinogen (group 1).

The human epidemiologic evidence was not consistent for all studies but did point to a generalized excess of all cancer mortality (without any pronounced site specificity) in four highly exposed industrial cohorts with well-documented exposure. Furthermore, in three of the cohorts studied, mortality from all cancers combined increased with higher estimated serum TCDD levels in a statistically significant manner. In the fourth cohort, the cancer excess was confined to those individuals with the longest duration of exposure.

TCDD is a multisite carcinogen in animals. However, it is not directly genotoxic and is thought to induce tumors in animals indirectly. TCDD operates via an Ah (aryl hydrocarbon) receptor that is present in many tissues in both animals and humans. In animals, the affinity of TCDD for the Ah receptor is correlated with carcinogenic potential. Animal carcinogenesis is thought to arise from Ah receptor-mediated alteration of gene expression, although other possible mechanisms, such as increased oxidative DNA damage or immune suppression, have been proposed. TCDD is also known to act as a promoter of other carcinogens. Body burdens of TCDD among the more highly exposed workers in the industrial cohorts were similar in magnitude to body burdens that produced cancer in rodent studies.

The hypothesis that the lymphatic and hemopoietic tissue is among the targets of the carcinogenic action of TCDD was first proposed after a series of case-control studies were carried out in Sweden in 1980. Elevated relative risks were found in several studies for non-Hodgkin's lymphoma and Hodgkin's disease. Animal experiments support the involvement of the lymphatic tissue.

From results so far obtained, the association to dioxin exposure with NHL would appear highly probable. More tentatively, Hodgkin's disease, multiple myeloma and leukemia are possibly linked to dioxin exposure.

Source: Journal of the National Cancer Institute Vol. 91, No. 9, May 5, 1999 and Leukemia (1999) 13, Suppl. 1, S72-S74.

Effects on children of exposure to pesticides

The neurobehavioral effects of pesticides, particularly organophosphates, carbamates, and organochlorine pesticides are a subject of increasing concern. A study carried out at the Bureau of Applied Research in Anthropology at the University of Arizona showed that young children exposed to pesticides were unable to draw a simple line picture of a person. The random undifferentiated lines drawn by exposed children averaged only 1.6 body parts per figure, whereas nonexposed children produced lifelike figures averaging 4.4 body parts each.

This simple test provided compelling evidence of possible neurodevelopmental effects of pesticides in children.

However, there has been criticism of the method used in collecting data for this study. One objection is that the data from the test were not accompanied by corresponding tissue or environmental pesticide concentrations but were based on the criteria of residential proximity to farms that used high quantities of organophosphates, organochlorine and pyrethroid compounds.

Nonetheless, the findings from the study have received considerable attention within the scientific community.

Ultimately, the challenges posed by neurobehavioral toxicology lie in refining tests of cognitive and developmental skill sets in exposed children, identifying additional contaminants and mechanisms for behavioral effects, and improving dose-response measures in a way that facilitates effective risk assessment. Epidemiology studies are also needed to integrate the results of psychological and toxicological testing with possible population-level effects. Many of these areas are currently active areas of research.

Source: Environmental Health Perspectives Vol. 107, No. 6, June 1999.

The management of anthrax in biological warfare

A working group comprising representatives from academic medical centers, public health and emergency management institutions and agencies in the United States has identified anthrax as one of the most serious diseases that might be used as a biological weapon. Research on this use of the disease began more than 80 years ago, and today it is thought that at least 17 countries have offensive biological weapons programs although it is uncertain how many involve the production of anthrax.

Bacillus anthracis is an aerobic, gram-positive, sporeforming, nonmotile Bacillus species. The nonflagellated vegetative cell is large (1-8 µm in length, 1-1.5 µm in breadth). Spore size is approximately 1 µm. Spores grow readily on all ordinary laboratory media at 37°C, with a "jointed bamboo-rod" cellular appearance and a unique "curled-hair" colonial appearance, and display no hemolysis on sheep agar. This cellular and colonial morphology theoretically should make its identification by an experienced microbiologist straightforward, although few practicing microbiologists outside the veterinary community have seen anthrax colonies other than in textbooks.

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as that found in the blood or tissues of an animal or human host. The rapidly multiplying vegetative anthrax bacilli, on the contrary, will only form spores after local nutrients are exhausted, such as when anthrax-infected body fluids are exposed to ambient air. Full virulence requires the presence of both an antiphagocytic capsule and 3 toxin components (i.e, protective antigen, lethal factor, and edema factor). Vegetative bacteria have poor survival outside of an animal or human host; colony counts decline to undetectable within 24 hours following inoculation into water. This contrasts with the environmentally hardy properties of the *B anthracis* spore, which can survive for decades.

Most experts concur that the manufacture of a lethal anthrax aerosol is beyond the capacity of individuals or groups without access to advanced biotechnology. However, autonomous groups with substantial funding and contacts may be able to acquire the required materials for a successful attack. One terrorist group, Aum Shinrikyo, responsible for the release of sarin in a Tokyo, Japan, subway station in 1995, dispersed aerosols of anthrax and botulism

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Animal and Human Carcinogens

Current data provided by the International Agency for Research on Cancer (IARC) and the US National Toxicology Program (NTP) indicate that there are approximately 75 agents known to be causatively associated with cancer in humans and a further 60 considered to be probably carcinogenic to humans. An additional 225 agents are considered by IARC as possibly carcinogenic to humans. This compares with the number of approximately 400 chemicals shown to be carcinogenic in animals.

Since some chemicals cause multiple site cancer in both sexes of each strain and species, whereas others may induce tumors in a single organ in one sex of only one strain of rodents, it is essential to evaluate data for each chemical.

More precise criteria than those currently used are needed for grouping chemicals considered to be carcinogenic to rodents or/and to humans. It is certainly misleading to designate all chemicals that induce cancer in animals as being equal and representing similar risks to humans.

Likewise, even though bioassays are indeed excellent surrogates for humans, not all chemicals shown to cause tumors in animals will, or should be expected to, prove to be carcinogenic to humans. Many reasons can be given for this lack of concordance, but a main one is that we should not expect the animal-to human concordance to be perfect, largely for the reason mentioned: not all animal carcinogens are equal (that is, not equally potent or equally carcinogenic). Thus, chemicals such as *d*-limonene or allyl isothiocyanate that induce tumors only in the male rat kidney or urinary bladder are not in either the IARC or the NTP listings of carcinogens and clearly do not represent the likely cancer hazards that other more striking multiorgan, multistrain, and multispecies carcinogens do. Conversely, we know that all human carcinogens that have been tested adequately in animals are also carcinogenic to laboratory animals.

Because many of the chemicals evaluated by IARC and the NTP are the same, while some are unique, it is not possible to simply add together numerical data from the two sources without individual comparisons.

Source: Environmental Health Perspectives Vol. 107, No. 7, June 1999.

FOOD CROPS: A TARGET FOR BIOLOGICAL WARFARE

The horror of biological weapons is usually portrayed in terms of intentional exposure of a human population to deadly diseases such as anthrax or plague. However, a less obvious type of biological weapon which targets an enemy's food crops is also a potentially devastating weapon of warfare and terrorism. All major food crops come in a number of varieties, suited to specific climate and soil conditions. These varieties have varying sensitivities to particular diseases. Crop pathogens, in turn, exist in different strains which will infect and damage individual crop varieties to differing degrees.

In biological warfare, an aggressor can isolate strains of pathogens that would attack only the enemy's sources of staple food.

A food crop epidemic initiated by a biological attack might look like a natural outbreak, thus freeing the covert aggressor from the risk of being immedietely identified.

Over the past 100 years, vigorous attempts have been made to develop international legal control of warfare, the recent ban on anti-personnel land mines being an example. Much of the emphasis has been on trying to minimize attacks on unprotected civilians, but anticrop warfare would have its greatest effects precisely against such people. An apparently anodyne form of warfare, with no explosions, bullets, mines or shrapnel, could, in reality, be terrifyingly effective in causing mass casualties.

In the 21st century, countries in both the developing and the developed world will still have much to fear from enemies – be they nations, political factions or terrorists – who may choose to engage in anticrop warfare. Most plant diseases that spread rapidly within a growing season have a short incubation period and visibly affect leaves. The strong agricultural extension service in the U.S., for example, can likely be counted on to identify a disease outbreak early, and it can prescribe costly pesticides to stop the flare-up. Such detection and control measures, however, require the kinds of resources that poorer countries often lack.

On the other hand, the developed nations of North America and western Europe have their own unique hazards because of the prevalent practice of growing only one or two varieties of major food crops. The lack of diversity in such monocultures renders the entire crop susceptible to organisms that are pathogenic to those varieties. An enemy could deliver the disease agents when weather conditions and the growth stage of the crop would best ensure a region-wide pandemic. Even if the victim nation successfully stopped the outbreak before widespread crop destruction occurred, it could suffer considerable economic losses.

The ongoing revolution in biotechnology and genetic engineering can extend the technical capabilities of anyone interested in developing biological weaponry, thereby increasing the threat.

A United Nations working paper has cited 10 international crop diseases as having weapons potential. Most of the world's key food crops are susceptible to these conditions, some of the most damaging being wheat rust, sugarcane smut and rice blast. Other crops at risk include corn, potatoes, numerous beans, various fruits and coffee. Pine trees, important economically for lumber, could also be targeted.

In the post-cold war era, political pressure and economic sanctions can be as significant as direct military confrontation; the mere power to drive economic resources toward stemming incipient epidemics gives anticrop warfare considerable importance. The prohibition of anticrop weapons should thus be a critical part of the current efforts to strengthen the Biological and Toxin Weapons Convention.

Source: Scientific American Vol. 280, No. 6, June 1999.

Increasing dietary calcium intake of children to help reduce morbidity due to environmental lead

Dietary calcium is well known to decrease gastrointestinal lead absorption and thereby reduce the risk of lead poisoning.

Young children 1-8 years old are at greatest risk of developing lead poisoning due to their low body weights (compared to adults), enhanced gastrointestinal lead absorption, greater hand to mouth activity, and their greater susceptibility to the effects of lead, particularly on the central nervous system.

The study of environmental lead on young children in inner-city areas of Bangkok, Thailand was reported in an earlier issue of this Newsletter (Vol. 5, No. 4, October 1995).

A recent study carried out in the United States has shown that lead-containing paint dust within older homes is the main source of lead exposure in children. This dust can be inhaled or ingested as a result of normal mouthing behaviours. However, absorption of lead via the gastrointestinal tract can be substantially reduced if the diet is relatively high in calcium.

The study focuses on young urban inner-city minority group children in Newark, New Jersey, and had as its objective the comparison of the calcium intakes of urban children at high risk of excessive lead exposure to the new dietary reference intakes (DRIs) introduced in August 1997 by the Food and Nutrition Board of the United States National Research Council.

Subjects were mothers and their children who were consecutive attendees receiving routine medical care at well-baby clinics or other community-based pediatric clinics. All participants were residents of the Newark, New Jersey area, including the contiguous communities of Irvington and East Orange. Most were residents of sections of Newark and adjacent communities previously identified as having significant sources of environmental lead using geographic information systems (GIS) technology. In addition, the target area has had a high incidence of pediatric lead poisoning for at least 30 years.

Children's dietary calcium intakes were assessed using a modified food frequency instrument targeted at the major food contributors of calcium. The instrument was adapted from a pediatric version of the National Cancer institute/Block food frequency questionnaire. It contained 14 items in which the parent was asked to describe the portion size and frequency of consumption of dairy foods and mixed foods containing dairy products, e.g., macaroni and cheese and pizza. One question asked about the presence of lactose intolerance.

Of the 314 children studied, 277 (88.2%) were members of African-American families, 28 (8.9%) were Hispanic, and 6 (1.9%) were members of white non-Hispanic families. The racial group was not identified for three children (0.9%). The mean age ± standard error (SE) was 3.5 ± 0.1 years. There were 175 children aged 1-3 years and 139 children aged 4.8 years. The percentages of males in the 1-3- and 4-8-year-old age groups were 53.7% and 50.7% respectively.

The mean ± SE calcium intake for 1-3-year-old children was 764±34 mg/day. The corresponding value for 4-8-year-old children was 739±36 mg/day. The percent of 4-8-year-old children not meeting the DRI for calcium (59.0%) was significantly (X^2, p = 0.001) greater than the proportion of 1-3-year-old children below the DRi (31.4%). The percentages of children with very low calcium intakes of less than 200 mg/day were 7.4% for the 1-3-year-old and 7.2% for the 4-8-year-old children, respectively.

Hispanic and African- American children in each age group had a similar incidence of calcium intakes below the DRI (32.0 and 29.4% for 1-3-year-old, and 60.5 and 63.6% for 4-8-year-old African-American and hispanic children, respectively). Attendance at well baby clinics did not appear to influence calcium ingestion because percentages below the DRI for 1-3-year-old children attending well-baby clinics (37%) were comparable to those attending other clinics (29%). They were also comparable for 4-8-year-old children attending well-baby clinics (52%) versus other clinics (63%). The DRIs set a tolerable upper level intake (UL) of 2,500 mg calcium/day for all age groups; only one child in the current study exceeded this value.

Mean calcium intakes of the 1-3-year-old (746 mg/day) and 4-8-year-old (739 mg/day) children in the current study are comparable to intakes of 750 mg/day for 1-2-year-old and 772 mg/day for 3-5-year-old children reported in a large nationwide survey. However, the range of dietary calcium intakes found in young children investigated in the current study is broader than those typically found in other recent studies. This may be due to differences in the composition of the target population in the various studies, or it could also reflect as yet unidentified factors specific to the Newark area that would require additional investigation. The broad range of intakes suggests that there are no methodological biases producing systematic errors that either overestimate or underestimate dietary calcium in the sample studied.

The mechanisms by which dietary calcium reduces gastrointestinal lead absorption have been studied extensively in experimental animals and, to a lesser extent, in people, and involve complex interactions among lead, dietary calcium, intestinal calcium binding proteins, and vitamin D, specifically 1, 25 dihydroxyvitamin D. These interactions explain why relatively large intakes of calcium are needed to reduce the gastrointestinal absorption of much smaller quantities of lead. Calcium may also provide protection against lead by other mechanisms because the toxic effects of lead are caused in part by its interference with calcium mediated cellular functions.

It could be argued that providing calcium supplements to children would be a better approach than trying to increase calcium intake from food. However, diets that are high in calcium-containing foods are also rich in other important nutrients. In addition, the data from the current study demonstrate that a considerable percentage of urban children will have high calcium intakes from food, even in the absence of a concerted community effort to promote an increase in dietary calcium in this age group. Thus, a public health program to increase consumption of high-calcium foods by urban children with currently low calcium intakes may be rewarding. Nevertheless, the use of calcium supplements can be an additional approach for increasing the dietary intake of calcium by urban children.

Source: Environmental Health Perspectives Vol. 107, No. 6, June 1999.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND LOW-LEVEL LEAD EXPOSURES IN CHILDREN

Lead is considered to be the single most significant environmental health threat to children in the United States today.

Low-level lead exposures can significantly impair cognitive and motor function in children, particularly if the exposures occur before the age of six. There is a general consensus among toxicologists that every increase in blood lead levels of 10 micrograms per deciliter (µg/dL) is associated with a one-to three-point drop in IQ. Although there is debate over the statistical validity of the association, a majority opinion holds that there is no threshold of effect in children, meaning that a level so low as to be without a measurable effect has yet to be identified. Lead-exposed children also exhibit behavioral problems and often have difficulty concentrating and staying focused.

Research findings over the last twenty years have contributed to the hypothesis that, at least in some cases, lead may play a role in the development of attention deficit/hyperactivity disorder (ADHD) in children. However, the role of lead in the etiology of ADHD is the subject of continuing investigation, since it is likely that many other risk factors may also be involved. These factors include genetic predisposition, material smoking and alcohol use, and complications during pregnancy.

A study is now under way of ADHD in a population of 8,000 children in North Carolina. This study will help to identify subpopulations in which the disorder is most prevalent and investigate possible causative factors including reproductive problems such as preterm delivery and pregnancy complication, as well as childhood lead levels.

Source: Environmental Health Perspectives Vol. 107, No. 6, June 1999.

HEALTH EFFECTS OF ARSENIC: RESEARCH ISSUES

All human populations are exposed to arsenic in one form or another since it is a naturally occurring element, present in food, soil, air and water. Of the various arsenical compounds, current evidence indicates that the inorganic arsenicals are more acutely toxic than most organic forms. It has been suggested that the chronic toxicity of many organic forms of arsenic, especially those found in fish and shellfish, is less than the inorganic forms of the element. Thus arsenobetaine, an organic arsenical from fish, is absorbed and excreted as the parent chemical and appears to exert little acute toxicity. The inorganic compounds however are acutely toxic and long term exposure in humans has been associated with various cancers.

At the present time, research into the carcinogenic potential of arsenic is impeded by the absence of clear animal models. Establishing animal models should be a priority area in research into the health effects of arsenic poisoning, since the development of whole-animal and cell culture systems for defining the carcinogenic processes for arsenic are critical to advancing current knowledge in this area.

Source: Environmental Health Perspectives Vol. 107, No. 7, June 1999.

The management of anthrax in biological warfare

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throughout Tokyo on at least 8 occasions. For unclear reasons, the attacks failed to produce illness.

The accidental aerosolized release of anthrax spores from a military microbiology facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 79 cases of anthrax infection and 68 deaths, and demonstrated the lethal potential of anthrax aerosols. An anthrax aerosol would be odorless and invisible following release and would have the potential to travel many kilometers before disseminating. Evidence suggests that following an outdoor aerosol release, persons indoors could be exposed to a similar threat as those outdoors.

In 1970, a World Health Organization (WHO) expert committee estimated that casualties following the theoretical aircraft release of 50 Kg of anthrax over a developed urban population of 5 million would be 250,000, 100,000 of whom would be expected to die without treatment.

However, recommendations regarding antibiotic and vaccine use in the setting of a biological warfare attack are conditioned by limited vaccine supplies and the limited current understanding of antibiotic resistance patterns.

A number of possible therapeutic strategies have yet to be fully explored. However, given the rapid course of symptomatic inhalational anthrax, early antibiotic administration is essential.

To develop an effective response to a biological warfare attack involving anthrax, the medical community requires new knowledge of the organism, its genetics and pathogenesis. Improved rapid diagnostic techniques and effective prophylactic and therapeutic regimens are also essential, together with an accelerated vaccine development effort.

Finally, an expanded knowledge base is needed regarding possible maximum incubation times after inhalation of spore-containing aerosols and optimal postexposure antibiotic regimens.

Source: JAMA Vol. 281, No. 18, May 12, 1999.

Immune Responses To Bacillus Thuringiensis Pesticides

A health survey was conducted recently in farm workers in the United States before and after exposure to Bacillus thuringiensis (Bt) pesticides. The Bt organism is used in microbial pesticides developed to avoid the toxicity associated with many chemical pesticides. Microbial pesticides have been used for large scale pest eradication for more than 30 years.

Bt is a gram-positive, spore-forming bacillus that is distinguished from *B. cereus* and *B subtilis* by the presence of a paraporal body (PIB) commonly referred to as the toxin crystal (cry).

Contemporary commercial *Bt* pesticide formulations are complex in composition; they contain large amounts of spores (> 10^9/mL of product) in close association with intact and partially assembled and/or degraded PIB crys, residual amounts of fermentation medium, cell wall debris, and trace amounts of vegetative cells.

Safety assessments of *Bt* have focused primarily on the potential pathogenicity of the organism and toxicity of the cry for mammalian species. Potential allergic reactions associated with the use of *Bt* have not been considered, although an alkaline protease produced by a related organism, *B. subtilis,* has been identified as a respiratory allergen and studied extensively because of occupational exposure in the detergent industry. Only one documented and three other questionable cases of overt human disease associated with *Bt* pesticide use have been reported. In this public health survey of a large number of individuals exposed to a massive *Bt* pesticide spraying program, some of the symptoms reported included rash and angioedema. One of the spray workers in this project developed dermatitis, pruritus, swelling, and erythema with conjunctival injection. *Bt* was cultured from the conjunctivae. In 1992 the use of *Bt* in an Asian gypsy moth control program was associated with classical allergic rhinitis symptoms, exacerbations of asthma, and skin reactions among exposed individuals reporting possible health effects after the spraying operation. Unfortunately, there was no follow up to determine whether these events were *Bt*-induced hypersensitivity or toxic reactions or merely due to common aeroallergens coincidental to the season during which the spraying occurred. Similar findings occurred during another *Bt* spraying in the spring of 1994. Allergenicity is of particular concern because approximately 75% of asthma cases are triggered by allergens and morbidity and mortality due to asthma have increased considerably over the past 20 years. Although the evidence thus far does not directly implicate human health risks with the use of *Bt*, it is clear that potential allergenicity of these strains should be evaluated. To accomplish this goal, a surveillance program was conducted in a group of farm workers before and after exposure to *Bt* pesticides.

Molecular genetic probes to identify *Bt* organisms isolated from these workers confirmed that both skin and antibody reactions were directed against the same *Btk* strain that was present in the commercial product used during current spray operations. Although respiratory, eye, and skin symptoms were reported by some workers, none of these symptoms could be attributed to previously established case definitions of occupationally related disease. The few ventilatory abnormalities detected by peak expiratory flow rate testing were found in heavy smokers. Nevertheless, the lack of clinical disease in this cross-sectional survey should be interpreted with caution because of the healthy worker effect, which might be more prevalent among migrant farm workers who, upon associating clinical symptoms with a particular crop or farm job, would likely seek employment in a different agricultural area. Moreover, clinical symptoms would not be anticipated unless there was repeated longterm exposure and more vigorous antibody responses to these organisms.

Although occupationally related clinical diseases were not observed in this cross-sectional survey, the fact that skin and serologic tests of immediate hypersensitivity developed in some workers indicates that adverse IgE mediated health effects could develop if repetitive exposures continue in some of these workers. Longitudinal surveillance studies will be necessary to establish whether this would occur. These results also suggest that future large-scale urban spraying of *Bt* pesticides may not be innocuous and may require more direct health monitoring and surveillance.

Source: Environmental Health Perspectives Vol. 107, No. 7, June 1999.

Mass Poisonings with PCB Mixtures

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A research priority is for studies in appropriate animal models (including wildlife animal models) to determine if there is a causal relationship between PCB congeners, endocrine changes, and developing neurologic parameters. Characterization of dose-response relationships should be a central objective of such studies.

Source: Environmental Health Perspectives, Vol. 107 Supp. 4, August 1999.

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