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Chulabhorn Research Institute

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".

Second Meeting of the Network for Scientific Cooperation in Environmental Toxicology

1 – 2 March 2001, Bangkok

This second meeting of the network members was organized by Chulabhorn Research Institute (CRI) and supported by United Nations Development Programme (UNDP). The two day meeting was attended by members of CRI and the institute's team of international experts together with delegates from 12 countries in the Asia/Pacific region.

On the first day of the meeting, delegates presented country reports on the status of environmental toxicology and the strengths and weaknesses of current approaches to protection of the environment in their respective countries. *Excerpts from these reports are on pages 4 – 5.*

The second day of the meeting was devoted to the discussion of possible strategies for future cooperation, including the establishment of regional advisory groups to deal with specific problems. Other proposed goals for network cooperation included joint-research, joint-teaching and exchange of scientific personnel.

There was also discussion on the operational procedures to be followed in an internet-based information exchange

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Second Meeting of the Network for Scientific Cooperation...

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service with linkages among network partners as well as to global sources of expertise. The delegates agreed on both a vision and a mission for the network.

The vision is to foster scientific cooperation and coordination among members of the network for the promotion of environmental toxicology towards sustainable development. And the network's mission is scientific cooperation in environmental toxicology to facilitate information generation and dissemination, human resource development, technical collaboration, technology advancement, and research collaboration for the sustainable development of countries in the Asia/Pacific region.

A New Approach to Toxicity Testing

A new approach to toxicity testing called "toxicogenomics" has grown out of the human genome project. Rather than using animal pathology to identify illnesses, it probes human or animal genetic material printed on plates – DNA arrays, for example. Toxicologists are using the technology to profile gene expression in cells exposed to test substances. Gene arrays containing thousands of genes that might be affected by toxic chemicals are used. These genes bind to matching genetic material extracted from animals or cell cultures exposed to the substance being tested. The extracted genetic material (messenger RNA) comes only from genes that are currently active. It is reverse-transcribed and tagged with a radioisotope or a fluorescent marker to simplify detection. Different colour markers can be used for material from treated cells and untreated controls. When these labelled sequences are tested on a single array, both treated and untreated types bind to a gene site, with the resulting colour at each site showing the degree to which that gene has been turned on or off by the test substance.

The great promise of toxicogenomics is that it might be used to scan the entire human genome to see which genes are affected by specific chemicals. An immediate goal is to look at different classes of substance and identify groups of genes that are correlated with known classes of toxicants. These genes could then be used for reduced testing, using a much-simplified set of DNA assays, to determine whether a test chemical exhibits any of several common toxicities. The biggest challenge will be interpreting the results of these analyses. Simply observing that a chemical changes a cell's gene expression is meaningless, as virtually any change in the environment will do that. The body makes complex cellular-level adjustments. It is not adequate simply to compare a test chemical's effects on gene expression to those of known toxicants. It is also necessary to validate the entire process by correlating such changes to actual illnesses.

A cautionary note, however, is that since these DNA tests are difficult to interpret, some toxicological hazards could be exaggerated and others underestimated.

Source: Chemistry & Industry, No. 5, March 2001.

Toxicity Testing and Public Opinion

The intensive lobbying by action groups against the use of animals for toxicity testing will make it increasingly difficult for agencies to obtain sufficient data for the conduct of a proper risk assessment of existing chemicals. However, potential alternatives or complementary strategies to current approaches do exist and need to be further developed and implemented.

The first priority is to develop models to estimate the nature and duration of human and environmental exposure to each chemical. As risk is directly related to exposure, testing requirements could be less rigorous if exposure is low.

A more targeted approach to toxicity testing should also be considered. This depends on a reliable database.

The rapid emergence of *in-vitro* tests provides scope for the detection of each chemical's ability to produce specific lesions. Human tissues may be used in such tests to make them more relevant for human risk assessment purposes.

Non-invasive monitoring methods may be used as early means of detection of adverse effects. They are also more acceptable than invasive methods on ethical grounds because they minimise the effects of stress on the parameters being measured. As examples, the following techniques have been applied in medicine but have yet to gain significant use in toxicity testing.

Nuclear magnetic resonance spectroscopy is used in visualisation of the morphology of soft tissues. However, equipment has been expensive and, until recently, the commercially-available instrumentation was not suitable for studies in small animals. A particular initial application is likely to be early detection of tumours in soft tissues and brain lesions.

There is also the potential to measure changes in many endogenous volatile substances emitted by an organism when exposed to a chemical. Commercial availability of robust equipment and an imaginative approach to the above techniques are necessary for their successful implementation.

Standardised test procedures are undoubtedly beneficial, but they can also lead to the use of scarce or expensive resources on inappropriate tests. Future emphasis is likely to be on the more effective use of a smaller number of animals and the termination of experiments before absolute toxicity occurs.

Source: Chemistry & Industry, No. 22, November 2000.

A Cautious Approach to the Global Campaign to Ban DDT

The treaty on persistent organic pollutants – POPs – was finalised at the United Nations Environment Programme meeting in Johannesburg in December 2000. It will be officially signed in Stockholm in May 2001. Of the 12 chemicals covered by the treaty, eight are pesticides, two are industrial chemicals and the rest are unwanted by-products of combustion and industrial processes. The majority of these will come under an immediate ban. However, the pesticide dichlorodiphenyltrichloroethane (DDT) is exempted because it is still essential in many tropical countries to kill malarial mosquitoes.

Malaria affects more than 300 million people worldwide, and every year it kills more than one million people. An estimated two dozen countries still find DDT effective for malaria control, so elimination of use of the chemical for this purpose should proceed cautiously.

Many alternatives to DDT have already been successfully used for controlling malaria. Mexico, for example, committed itself to ending use of DDT by 2007, provided that suitable alternatives are available. Relying on a range of effective and affordable chemical and non-chemical strategies, Mexico has been so successful that its DDT manufacturing plant has ceased production owing to lack of demand. Similar success stories of effective programmes not based on DDT can be found around the globe.

The cautious approach being adopted in the treaty reflects uncertainty about how many countries that are still using DDT can successfully move from it. South Africa illustrates the dilemma. South Africa stopped spraying DDT out of concern for its hazard to human health. But one of the mosquito vectors of malaria proved resistant to synthetic pyrethroid sprays, so South Africa has resumed using DDT. South Africa made the difficult choice that the developmental risks from spraying with DDT are outweighed by the need to provide protection from malaria.

The treaty on persistent organic pollutants raises a series of equity challenges that must be addressed directly. Firstly, the countries still relying on DDT include some of the poorest in the world. These countries must have financial and technical assistance from the developed world to strengthen their ability to control malaria. The feasibility and cost of shifting from DDT must be assessed and requisite investments made. The WHO's action plan for reducing reliance on DDT calls for such assessments and capacity building activities.

Secondly, the interests of those countries for which alternatives are not available must also be protected. Only two countries still produce DDT – India and China. India's malaria control programme, with support from the World Bank, expects to reduce its use of DDT. Concomitant with increased investments in researching and implementing alternatives to DDT, steps must be taken to assure that DDT remains available at an affordable price to those countries that truly need it. Such supplies would need to be carefully distributed and monitored, to prevent diversion of DDT to illegal agricultural uses.

Malaria imposes a horrendous social and economic burden totalling billions of dollars. The treaty on persistent organic pollutants can mobilise fresh financial and technical resources to help achieve protection from both malaria and DDT.

Sources: BMJ, Vol. 321, December 2000 and Chemistry and Industry, No. 24, December 2000.

NEW TREATY ON PERSISTENT ORGANIC POLLUTANTS

The treaty on persistent organic pollutants (POPs) was finalized by representatives of 122 countries at a meeting in Johannesburg, South Africa, in December 2000.

The treaty will either ban or phase out 12 long-lived pesticides and other toxic chemicals still used in many developing countries.

The POPs treaty was organized by the United Nations Environment Programme to address the substances that have come to be known as the "dirty dozen" namely: DDT, Aldrin, Dieldrin, Endrin, Chlordane, Heptachlor, Hexachlorobenzene, Mirex, Toxaphene, Dioxins/Furans and PCBs.

These substances get carried by global weather patterns to the polar regions, where they've been blamed for a variety of problems in wildlife and people. High levels of polychlorinated biphenyls (PCBs) in the breast milk of Inuit women, for example, have raised concerns about possible immunological and intellectual deficits in children. And according to one controversial theory, trace levels of POPs acting as "endocrine disrupters" may contribute to problems such as lower sperm counts and cancer in the general population.

The United States and most other developed countries banned PCBs and most POP pesticides years ago. However, they're still widely used in places such as India and Latin America. The treaty finalized last December would ban eight of these pesticides immediately. Two industrial byproducts on the list, dioxins and furans, will be reduced right away and eventually eliminated "where feasible," for example, by clamping down on open trash burning. PCBs, used in electrical transformers, will be allowed until 2025 as long as equipment is maintained to prevent leaks. To help developing countries destroy stockpiles and develop alternatives, delegates also agreed to an estimated $150 million annual fund run by the U.N.'s Global Environment Facility. The treaty will be signed in May 2001 in Stockholm and goes into effect once 50 countries have ratified it.

Source: Science, Vol. 290, No. 5499, December 2000.

Second Meeting of the Network for Scientific Cooperation in Environmental Toxicology

Excerpts from Country Reports

BRUNEI DARUSSALAM

"Availability of human resources is always a prime concern. In the Environment Unit there are 7 officials including the Head of Unit, and 8 clerical and technical support staff.

The Unit is tasked to handle domestic environmental issues such as solid waste, preservation of ecosystem, environmental awareness, and assessment of industrial development on environment, as well as regional matters such as ASEAN Working Groups on environment and global concerns.

The strategy is therefore to prime-up other departments within the Ministry of Development, such as the Public Works Department, and those outside the Ministry, such as the Ministry of Health and Ministry of Industry and Primary Resources, to work together for the environment.

However such arrangements at times also encounter problems since those departments face the same man-power constraints. When faced with conflicting demands on manpower resources, their primary duty would be to accomplish the department's priority."

CAMBODIA

"In the area of agriculture, the upward trend of utilization of chemical pesticides and fertilizers is of increasing concern of environmental pollution problem in Cambodia, particularly water pollution and ecology degradation caused by residues of these chemicals. The banned pesticides have been imported continuously and illegally, and freely sold at markets throughout the country. But, to date, information on chemical pesticide and fertilizer usage is not available, due to failures in the implementation of pesticide registration and management."

CHINA

"In recent years, large quantities of chemicals have gone into the environment because of industrial development. The combined effects of various chemical mixtures should be considered. The investigation on the reproductive and developmental effects and carcinogenic effects by the environmental endocrine disrupters, though just started, has been paid much attention to by toxicologists in our country. Considering the characteristics of environment pollution in China, the importance in environmental endocrine disrupter study may be in the agricultural chemicals, synthetic estrogens used in birth control, organic tin in the ocean and detergents. It may become a focus for research in environmental toxicology in the future."

INDONESIA

"Environmental toxicology problems in Indonesia cover various aspects as described below:

- Increase in the use of hazardous substances in industrial and domestic contexts.
- Lack of information and untrained government officials in environmental toxicology, specifically in hazardous substance management.
- Some industries still lack an environmental management system in handling their hazardous substance products."

LAO PDR

"Much of the pollution from heavy metals stems from small and medium enterprises. One example is dyeing sludge from garment factories and other textile enterprises, which mostly contain cobalt in different concentrations. Another example are furniture shops, which use lacquer and varnish. Residues are usually disposed of along the road sides and into gutters. Although small scale pollution like this does not seem to be a problem at present, the accumulative nature of heavy metals will lead to future problems."

MALAYSIA

"Although there are sufficient number of laboratories capable of performing a wide range of standard chemical analysis, there are only a small number that can carry out residual organic analysis. Examples of such residual analysis include analysis for persistent organic pollutants (POPs) or endocrine disrupting chemicals (EDCs) at very low concentrations.

There is no monitoring of POPs and EDCs in the environment as the potential generating sources are considered relatively small in number at this time. However, there is every possibility that the current scenario may change."

MONGOLIA

"Cases of the pollution of soil and water in bigger settlements and cities of Mongolia with toxic chemicals above the national maximum allowable concentration (MAC) still occur. The main sources of the increased pollution of water, air and soil in cities are the toxic gas containing chemicals produced by solid and liquid fuel combustion, solid and liquid waste of mining and other processing industries and production and service units, evaporation and loss of chemicals and chemical products used in the industry and units and the chemicals remaining in the final waste products."

PHILIPPINES

"Industrialization of the country coupled by the unabated population growth is continuously causing adverse environmental changes leading to serious health consequences. Conditions such as inadequate water supply, poor sanitation and unsafe food; poor housing and shelter; air, water and soil pollution; unacceptable disposal of toxic and hazardous wastes, remain a primary environmental health challenge. Trade and industrial policies that favor uncontrolled influx of hazardous chemicals, whether natural or synthetic, have largely contributed to these problems."

SINGAPORE

"As industries in Singapore developed and diversified into specialist chemical and other high technology processes over the years, the quantity and variety of chemicals produced, imported, transported, stored and handled has increased. To minimize the risks an extensive programme has to be implemented to ensure the population is not at risk. Some of these industries also generate toxic wastes that need to be either treated or disposed of in a safe manner."

SRI LANKA

"Our experience is that, in most places, chemicals are handled without any compliance to safety. In many instances, the workers and management are not aware of the hazards and safety of chemicals and therefore adequate precautions are not taken. In addition, the legal provisions and guidelines on chemical safety are old and have not been updated to suit modern standards. Provision of information and training of chemical handling workers are not usually carried out because this is not a legal requirement. Labelling of chemicals and need for MSDS is not in the statutes. Also the Department of Labour lacks expertise on inspection of chemical installations. The Division of Occupational Hygiene also lacks expertise and facilities to perform environmental and biological monitoring of chemicals."

From left to right: Dr. Phan Quynh Nhu, Dr. Nguyen Thi Kim Thai – *Vietnam*; Dr. Monthip S. Tabucanon – *Thailand;* Mr. Rajaratnam Rathamanoharan – *Sri Lanka;* Prof. Choon Nam Ong – *Singapore;* Dr. Erle S. Castillo – *Philippines* and Dr. Lubsanbazar Narantuya – *Mongolia*

THAILAND

"Organochlorine pesticides have been widely used in agriculture. This group of pesticides stays in the environment for a long time, especially as residues in soil that may flow to water resources. Major rivers in Thailand are believed to be contaminated with organochlorine, thus posing a threat to human health."

VIETNAM

"Environmental problems have brought about difficult challenges for Vietnam against the background of a poor country: serious degradation of the environment, long-term harmful effects caused by many years of war on the environment and nature, urgent social problems like poverty, disease, illiteracy, malnutrition etc. ... all need to be addressed at the same time, whereas investment sources are very limited."

ANNOUNCEMENT

Chulabhorn Research Institute

Training Workshop
Environmental & Health Risk Assessment and Risk Management of Toxic Chemicals

3 – 11 December 2001, Bangkok, Thailand

This course will be taught by a team of international experts as part of the Institute's UNDP supported program on Capacity Building in Environmental Toxicology and Technology and Management to Promote Sustainable Development in Asia and the Pacific

Transfer of knowledge and explanation of concepts and practices will be by means of plenary sessions and discussion followed by small group participation in selected case studies under the guidance of the team of experts.

The topics will cover the following areas:

1. Concept and Process of Health Risk Assessment
2. Hazard Identification
3. Dose-Response Assessment
4. Exposure Assessment
5. Risk Characterisation
6. Environmental Guidelines/Standards
7. Risk Management and Reduction
8. Risk Perception and Communication
9. Examples of Application Fields: air pollution, waste incineration, and agricultural pesticides

Registration Fee US$650

Further information can be obtained from:

Office of Academic Affairs
Vibhavadee-Rangsit Highway
Bangkok 10210, Thailand
Tel: (66-2) 574-0622 to 33 ext. 1610
Fax: (66-2) 574-0616 or (66-2) 247-1222

PLEASE NOTE THE CHANGE OF DATES

(this course was previously scheduled to take place from 8 – 16 October)

ENVIRONMENTAL HEALTH RISK FOR TRAFFIC POLICE IN THAILAND

Air pollution from vehicles, which causes dangerous effects on human health and on the environment, is composed of carbon monoxide, hydrocarbon compounds, lead, nitrogen oxides, sulphur dioxide and also dust particles.

Noise pollution from vehicles also has a negative effect on human health. These factors can lead to physical and mental health problems. Traffic police in particular face many health problems as a result of pollution from vehicles. A recent study of the health of traffic police in the Bangkok metropolitan area found that they suffered from psychological stress to the extent that 15.87% had a risk of mental health problems.

Every traffic policeman had some illness, especially respiratory disease and other illnesses such as headache, insomnia and stomachache; sometimes mental health illness as well. It was also found that the main physical health problems seen among traffic policemen at the out-patient department of the Police Hospital in 1992 were hearing problems (34.68%), a high blood lead level (31.3%), respiratory problems (23.3%), liver problems (16.95%), hypertension (9.3%) and renal problems (4.61%).

Factors associated with reduced pulmonary functions were examined in policemen in the Bangkok metropolitan area. Pulmonary tests were performed using a Vitalograph spirometer. The study group comprised 174 traffic policemen, with 173 policemen with desk jobs as the control group. The result of the study was that 44 traffic policemen (25.29%) had decreased pulmonary function.

A cross-sectional study was conducted to assess whether traffic policemen working in the Thonburi district of Bangkok had poorer respiratory health than the average Thai population. The benefits of using masks as a preventive measure countering the respiratory hazards of air pollution were assessed. Traffic policemen (n=629) who had worked in Thonburi and normal male subjects (n=303, the control group) were evaluated for respiratory symptoms using the British Medical Research Council questionnaire. Their respiratory function was measured by spirometry. Only non-smokers were included in the final analysis, which revealed that traffic policemen (n=242) suffered significantly more from cough or phlegm (P=0.005) and had more symptoms of rhinitis than control subjects (n=129). The traffic policemen had a significantly higher prevalence of abnormal air flow than the control group (P=0.04). Traffic policemen who did not use protective masks had not only a significantly higher prevalence of abnormal FEV_1 (Forced Expiratory Volume in the first second) but also a significantly higher prevalence of FVC (Forced Vital Capacity) than the control group (P=0.046). They also had higher relative risks of abnormal FEV_1 and FVC results than those who used protective masks.

The results of the study suggest that traffic policemen should be supported by well-managed air pollution protection measures.

Source: Asian-Pacific Newsletter on Occup. Health and Safety, March 2001.

PUBLIC HEALTH CHALLENGE OF INDOOR AIR POLLUTION IN DEVELOPING COUNTRIES

A recent report on the health effects of indoor air pollution in developing countries has confirmed the findings of previous reviews which have associated such pollution with a range of serious and common health problems.

The most important appear to be childhood acute lower respiratory infections, which remain the single most important cause of death for children aged under 5 years in developing countries. Nevertheless, the evidence has significant limitations: a general paucity of studies for many conditions, a lack of pollution/exposure determinations, the observational character of all studies, and the failure of too many studies to deal adequately with confounding.

That few studies have measured pollution or exposure presents the possibility of serious misclassification of exposure, and means that very little information is available to quantify the relationships between exposure level and risk. This has important implications for assessing the health impact of exposure levels in various populations, as well as in estimating the potential health gains that might result from reducing exposure by different amounts. In particular, it should be noted that where interventions (mainly stoves) have been evaluated the residual levels of pollution are still well above those indicated in current air quality guidelines. The observational nature of most studies presents a problem in relation to confounding since households adopting less polluted stoves and/or behaviour generally do so following improvements in their socio-economic circumstances, which strongly influence many health outcomes. This, together with inadequate adjustment for confounding in a substantial proportion of studies, is likely to result in biased risk estimates.

Despite these limitations, the evidence for two of the most important conditions – acute upper respiratory infections and chronic obstructive respiratory infections and chronic obstructive respiratory disease – is compelling and suggestive of causality, particularly in conjunction with findings for environmental tobacco smoke and ambient pollution. With these out-

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Air Pollution and Reproductive Health

Air pollution in the Czech Republic is primarily the result of the use of brown coal which has high sulfur content. Sulfurdioxide emissions have increased from 0.9 million tons in the 1950s to 3.5 million tons by 1985.

During the 1980s, ambient SO_2 levels associated with high levels of particulate matter (PM) in the Teplice district of Northern Bohemia frequently exceeded U.S. and Czech air pollution standards in winter, when the use of coal increases and thermal inversions favor retention of the air pollution in the valley.

The Teplice Program, an international research program, was initiated in 1991 in response to concerns over potential health effects of this pollution. This program sponsored cooperative research among the Czech Institute of Hygiene, the Czech Ministry of the Environment, and the U.S. Environmental Protection Agency to compare health status in Teplice district to that in Prachatice district, chosen because of its relatively cleaner air. A critical component of this program was the establishment of air monitoring in both districts to measure aerosol and gas-phase air pollutants [PM, including volatile and semivolatile polycyclic aromatic hydrocarbons (PAHs) and toxic metals] as well as SO_2, nitrous oxides (NO_x), and carbon monoxide on an ongoing basis. Monitoring confirmed that levels of these air pollutants were considerably higher in Teplice than in Prachatice, and were higher in the winter than during the rest of the year in both districts. The Teplice Program includes studies of a number of health outcomes, including respiratory and neurologic effects in children, biomonitoring of mutagens in adults, and reproductive health in pregnant women and young men. Reproductive health studies were prompted by reports that rates of conception and incidence of congenital anomalies were affected by seasonal increases in air pollution.

In order to examine the possible relationship between seasonal elevated air pollution and male reproductive health, a comparison was made of 18 year old males living in Teplice and a matched cohort of volunteers from Prachatice.

Surveys were scheduled for either late winter, after the season of higher air pollution, or at the end of summer, when pollution was low. Participation included a physical examination, donation of a semen sample, and completion of a questionnaire on health, personal habits, and exposure to solvents and metals through work or hobby. Analysis of data from 408 volunteers showed that the men from Teplice and Prachatice were similar in physical characteristics, personal habits, and work- or hobby-related exposures. Sixty-six percent (272) of these men donated a single semen sample for routine semen analysis, computer-aided sperm motion analysis, and sperm chromatin structure assay. The mean (median) sperm concentration and sperm count were 61.2 (44.0) million/mL semen and 113.3 (81.5) million, respectively, and were not associated with district of residence or period of elevated air pollution. However, periods of elevated air pollution in Teplice were significantly associated with decrements in other semen measures including proportionately fewer motile sperm, proportionately fewer sperm with normal morphology or normal head shape, and proportionately more sperm with abnormal chromatin. These results suggest that young men may experience alterations in sperm quality after exposure to periods of elevated air pollution, without changes in sperm numbers.

Source: Environmental Health Perspectives, Vol. 108, No. 9, September 2000.

Public Health Challenge of Indoor Air Pollution in Developing Countries

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comes, the major weakness in the evidence relates to the quantification of the exposure-response relationship. For other health out-comes, including asthma, otitis media, lung cancer (particularly in relation to biomass fuel smoke) and nasopharyngeal/laryngeal cancer, interstitial lung disease, low birth weight, perinatal mortality, tuberculosis and cataract, the evidence must be seen as more tentative.

A few well-conducted randomized controlled studies on the health impact of reducing exposure would markedly strengthen the evidence, and should be feasible at the household level. For conditions where the evidence is very limited (e.g. low birth weight) or where a long latent period would make an intervention study impractical (e.g. tuberculosis, cataract), further observational studies are desirable.

Although work on interventions to reduce exposure has given mixed results, there is a wide range of possibilities and there has been some success in terms of both exposure reduction and uptake. The development and evaluation of interventions should take account of the many aspects of household energy supply and utilization, and should include assessment of pollution and exposure reductions, fuel efficiency and impact on the local and global environment, safety, capacity to meet household needs, affordability and sustainability. There is a need for a coordinated set of community studies to develop and evaluate interventions in a variety of settings, together with policy and macroeconomic studies on issues at the national level, such as fuel pricing incentives and other ways of increasing access by the poor to cleaner fuels. Also required is a systematic, standardized approach to monitoring levels and trends of exposure in a representative range of poor rural and urban populations.

Source: Bulletin of the World Health Organization, Vol. 78, No. 9, 2000.

Botulinum Toxin as a Biological Weapon

Botulinum toxin is the most poisonous substance known. A single gram of crystalline toxin, evenly dispersed and inhaled, would kill more than 1 million people, although technical factors would make such dissemination difficult. The basis of the phenomenal potency of botulinum toxin is enzymatic; the toxin is a zinc proteinase that cleaves 1 or more of the fusion proteins by which neuronal vesicles release acetylcholine into the neuromuscular junction.

Terrorists have already attempted to use botulinum toxin as a bioweapon. Aerosols were dispersed at multiple sites in downtown Tokyo, Japan, and at US military installations in Japan on at least 3 occasions between 1990 and 1995 by the Japanese cult Aum Shinrikyō. These attacks failed, apparently because of faulty microbiological technique, deficient aerosol-generating equipment, or internal sabotage. The perpetrators obtained their *C botulinum* from soil that they had collected in northern Japan.

Some contemporary analyses discount the potential of botulinum toxin as a bioweapon because of constraints in concentrating and stabilizing the toxin for aerosol dissemination. However, these analyses pertain to military uses of botulinum toxin to immobilize an opponent. In contrast, deliberate release of botulinum toxin in a civilian population would be able to cause substantial disruption and distress. For example, it is estimated that a point-source aerosol release of botulinum toxin could incapacitate or kill 10% of persons within 0.5 km downwind.

Any outbreak of botulism should bring to mind the possibility of bioterrorism. The availability and speed of air transportation mandate that a careful travel and activity history, as well as a careful dietary history, be taken. Patients should also be asked whether they know of other persons with similar symptoms. Absence of a common dietary exposure among temporally clustered patients should suggest the possibility of inhalational botulism.

Botulism can be prevented by the presence of neutralizing antibody in the bloodstream. Passive immunity can be provided by equine botulinum antitoxin or by specific human hyperimmune globulin, while endogenous immunity can be induced by immunization with botulinum toxoid.

Use of antitoxin for postexposure prophylaxis is limited by its scarcity and its reactogenicity. Because of the risks of equine antitoxin therapy, it is less certain how best to care for persons who may have been exposed to botulinum toxin but who are not yet ill. In a small study of primates exposed to aerosolized toxin in which supportive care was not provided, all 7 monkeys given antitoxin after exposure but before the appearance of neurologic signs survived, while 2 of 4 monkeys treated with antitoxin only after the appearance of neurologic signs died. Moreover, all monkeys infused with neutralizing antibody before exposure to toxin displayed no signs of botulism. In a balance between avoiding the potential adverse effects of equine antitoxin and needing to rapidly neutralize toxin, it is current practice in foodborne botulism outbreaks to closely monitor persons who may have been exposed to botulinum toxin and to treat them promptly with antitoxin at the first signs of illness. To facilitate distribution of scarce antitoxin following the intentional use of botulinum toxin, asymptomatic persons who are believed to have been exposed should remain under close medical observation and, if feasible, near critical care services.

Additional research in diagnosis and treatment of botulism is required to minimize its threat as a weapon. Rapid diagnostic and toxin typing techniques currently under development would be useful for recognizing and responding to a bioterrorist attack. Although polymerase chain reaction assays can detect the botulinum toxin gene, they are unable, as yet, to determine whether the toxin gene is expressed and whether the expressed protein is indeed toxic. Assays that exploit the enzymatic activity of botulinum toxin have the potential to supplant the mouse bioassay as the standard for diagnosis. Detection of botulinum toxin in aerosols by enzyme-linked immunosorbent assay is a component of the US military's Biological Integrated Detection System for rapid recognition of biological agents in the battlefield.

The competing needs for immunity to weaponized botulinum toxin and for susceptibility to medicinal botulinum toxin could be reconciled by supplying human antibody that neutralizes toxin. With a half-life of approximately 1 month, human antibody would provide immunity for long periods and avoid the reactogenicity of equine products. Existing *in vitro* technologies could produce the stockpiles of fully human antibody necessary both to deter terrorist attacks and to avoid the rationing of antitoxin that currently would be required in a large outbreak of botulism. A single small injection of oligoclonal human antibodies could, in theory, provide protection against toxins A through G for many months. Until such a product becomes available, the possibilities for reducing the population's vulnerability to the intentional misuse of botulinum toxin remain limited.

Source: JAMA, Vol. 285, February 2001.

The ICEIT NEWSLETTER is published quarterly by the International Centre for Environmental and Industrial Toxicology of the Chulabhorn Research Institute. It is intended to be a source of information to create awareness of the problems caused by chemicals. However, the contents and views expressed in this newsletter do not necessarily represent the policies of ICEIT.

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