IPCS News

The Newsletter of the International Programme on Chemical Safety

Issue 12 June 2000

A new director for IPCS

Congratulations to Dr Tim Meredith, who took up his functions as the new director of the IPCS in February 2000. However, he is no stranger to the Programme, having been involved in many of its activities over the past decade, particularly those in the field of poison control.

After graduating in medicine from Cambridge University, England in 1975, he embarked on a career in the UK National Health Service, specializing in general medicine and clinical toxicology. After a period of secondment to IPCS in 1989, he then joined the UK Civil Service where he served as a Senior Medical Officer in the Department of Health (DH). He held two appointments that were subsequently to make him well suited to become the new leader of the IPCS. From 1989 to 1992, he ran the Clinical Toxicology/Environmental Chemicals Section of the Health Effects on Environment and Food Division, where he worked on national policy formation relating to chemical safety. Following his involvement in the international preparations for the 1992 Earth Summit in Rio de Janeiro, he was made Head of the World Health Branch of the DH International Relations Unit. Over the next three years, he became closely involved in the activities of the governing bodies of WHO and participated regularly in the work of the WHO Executive Board, as well as continuing an involvement in clinical toxicology.

In 1995, Tim Meredith moved to the USA where he was appointed Professor of Medicine and Pathology and became the founding Director of the Center for Clinical Toxicology at Vanderbilt University, Nashville, Tennessee. His recent move to Geneva will means less bluegrass music for him, but he tells us that this "will be more than compensated for by a return to European weather and an opportunity to test personally the chemical safety of European cuisine!". ◆

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Endocrine disruptors

Endocrine disruptors (EDCs) are chemical substances thought to interfere with the functions of the body under the control of the hormonal system. Investigations have revealed effects on wildlife populations that may be the result of exposure to such chemicals present at low concentrations in the environment. Among these effects are malformed sex organs, changed sexual behaviour and infertility. There is a possibility that in humans, too, some effects on the reproductive system are the consequence of exposure to EDCs. ◆

For full article and details of IPCS activities in this area, see pages 4-5.

Microbial pest control

The IPCS has published over 50 evaluations of chemical pesticides in the Environmental Health Criteria series since the series started in 1976. It is perhaps a sign of the times that it has now just published its first evaluation of a biological pesticide.

Bacillus thuringiensis is an anaerobic spore-forming bacterium, the products of which have been used commercially as microbial pest control agents for the past 30 years. Their worldwide use is on the increase and the commercial production is now about 1% of that of chemical pesticides.

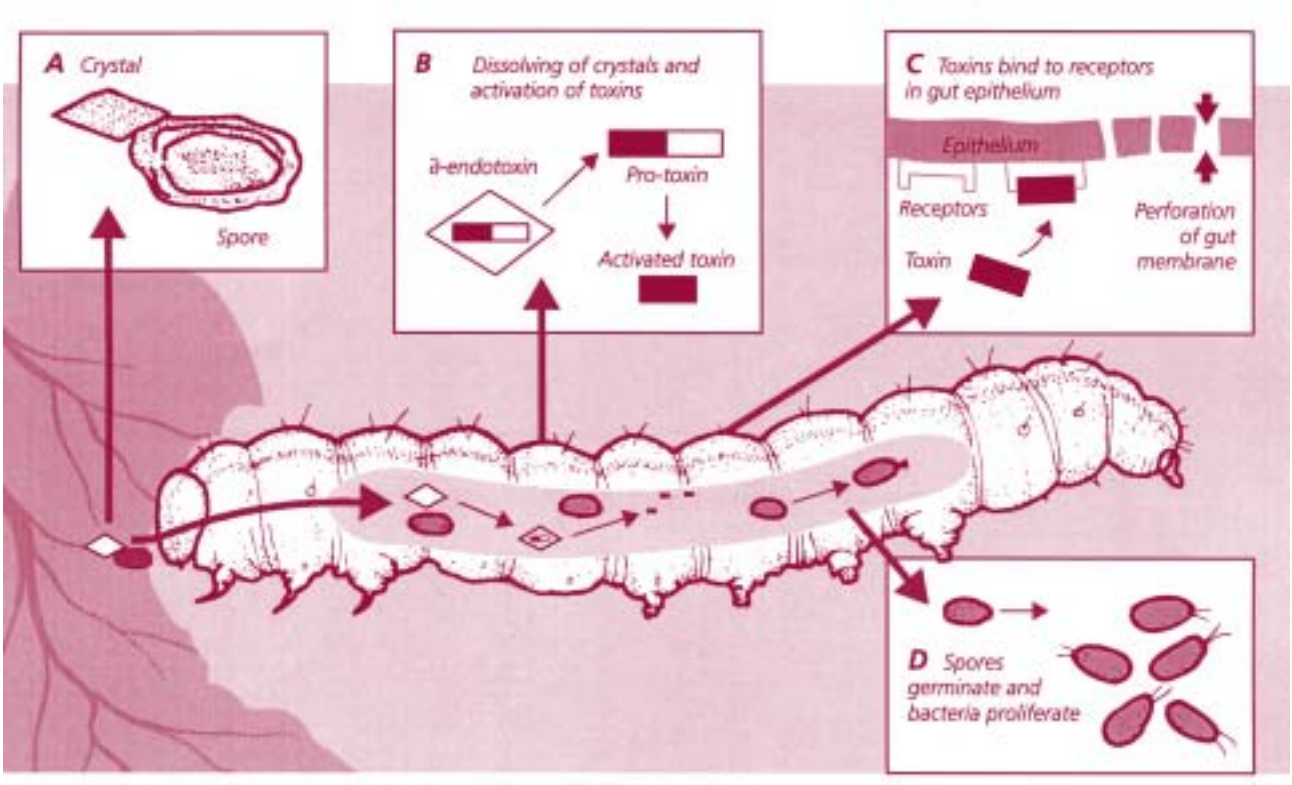
This species of bacterium has the unusual property of synthesizing toxic chemicals in the form of so-called insecticidal crystal proteins (ICP), which are attached to its spores. When these proteins are ingested by a susceptible insect larva they are solubilized and converted to an active toxin in the midgut, where they cause pore formation and lysis of the epithelial cells. This leads to favourable conditions for the bacterial spores to germinate. The resulting vegetative cells multiply in the larva's haemocoel causing septicaemia, and this can contribute to the death of the insect.

B. thuringiensis products generally contain both ICP and viable spores. Each year around 13 000 tonnes are produced worldwide, mostly in China, using fermentation technology. They are used against a variety of insect pests of forests and agricultural crops, including cotton, maize, potatoes and tomatoes. After spraying, the ICP becomes inactive within hours or days, but the spores may persist for months or years.

The insecticidal activity of *B. thuringiensis* products is highly specific for *Coleoptera* (beetles), *Diptera* (flies) and *Lepidoptera* (moths and butterflies), and there are no adverse effects on other insects, such as honey-bees, or on earthworms. The products have been used in large-scale programmes to control mosquitos, including the malarial vector *Anopheles sinensis*. They have also been used in the Onchocerciasis Control Programme in West Africa where, from 1982 to 1997, more than 5 million litres were sprayed on 50 000 km of rivers to control blackflies, the vector of the filarial worm that causes river blindness.

The IPCS evaluation examined the effects of *B. thuringiensis* products on laboratory mammals, as well as birds and fish. There were no adverse effects provided that no contaminating toxins, which can be produced by some subspecies during vegetative growth, were present. The field application of the products can result in considerable aerosol and dermal exposure of workers, as well as contamination of drinking-water reservoirs and food. However, human volunteers who ingested and inhaled large quantities of a formulation experienced no adverse health effects. Thus, *B. thuringiensis* products are unlikely to pose any hazard to humans or other vertebrates. ◆

The IPCS evaluation has just been published as Environmental Health Criteria 217: Bacillus thuringiensis. Further information on this subject may be obtained from Dr A. Aitio, IPCS (Fax: +41 22 791 48 48; E-mail: aitioa@who.ch).



Michel Mercier

Following his retirement as Director of IPCS in December 1998, Dr. Michel Mercier has taken on new challenges to continue to devote himself to helping humankind attain a better life through improving the quality of the environment. After achieving high academic degrees in industrial pharmacy, clinical biology and pharmaceutical sciences, he embarked on a 40-year career in academia and both the public and private sectors. From 1980 until his retirement from WHO, he provided leadership and direction to the IPCS. Having joined the programme only six months after its inception, he has been the driving force that shaped and built the programme into the highly respected organization that it is today. He played a vital role in conceiving and building the Intergovernmental Forum on Chemical Safety, serving also as its Executive Secretary from 1994 to 1997.

Several prestigious professional bodies around the world have honoured Michel Mercier. Notable was

"Think like a man of action, act like a man of thought"
Henri Louis Bergson (1859-1941)

his appointment as an Honorary Member of the Society of Toxicology in 1998, the top honour in his professional field. In Belgium, his home country, appointments to Orders of Chivalry have honoured him.

Throughout his professional career, Michel Mercier has constantly thought like a man of action, and acted like a man of thought. Since he continues to serve with appointments as Senior Special Fellow with the UN Institute for Training and Research, Liaison Officer to WHO at the International Life Sciences Institute, Scientific Adviser to the International Council on Metals and the Environment, and Associate Professor at the Department of Occupational Medicine and Environmental Hygiene, University of Montreal, he looks like being even busier in his "retirement" than he was during his long career. We wish him every success in his new endeavours. ◆

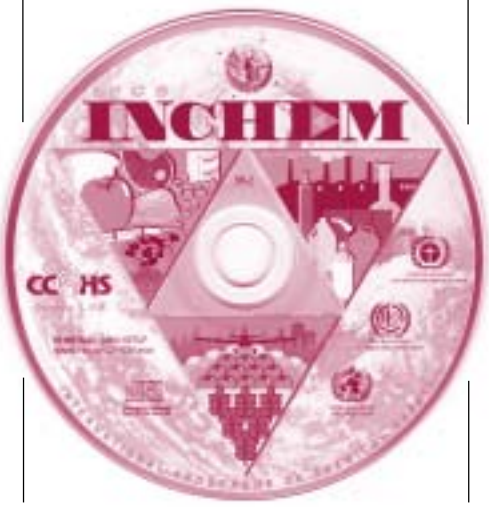
Roy Hickman

Michel Mercier can be contacted at Safework (Office 7-103), International Labour Office, 1211 Geneva 2 (tel:+4122 7996497; E-mail: mercier@ilo.org).

INCHEM

The IPCS INCHEM database contains the vast majority of the chemical safety data produced by the IPCS, including, in searchable form, tens of thousands of pages from the following ten series:

- Environmental health criteria monographs
- Health and safety guides
- Concise international chemical assessment documents
- International chemical safety cards
- Pesticide data sheets
- Toxicological evaluations of pesticides
- Toxicological evaluations of food additives and contaminants
- Toxicological evaluations of residues of veterinary drugs in food
- Poison information monographs
- Antidote monographs



The database is commercially available, both in CD-ROM and on the Web, on a subscription basis. The cost is US$ 500 for a single user. However, it is hoped that in the future the IPCS can identify donor funds which will allow free access on the Web to CD users and distribution of the CD-ROM without a subscription being required. ◆

For further information, including how to order, contact the Canadian Centre for Occupational Safety and Health, Customer Services, 250 Main Street East, Hamilton, Ontario, Canada L8N 1H6 (e-mail custserve@ccohs.ca) or visit the web site www.inchem.org.

Endocrine disruptors

A number of chemical substances are thought to interfere with the functions of the body that are governed by the hormonal system.

During the past decade there has been increasing concern and public debate regarding the potential adverse effects of environmental contaminants often referred to as *endocrine disruptors* (EDCs). These chemicals may interact with the endocrine system of humans and wildlife, and interfere with its normal functioning. The endocrine system is a complex, chemical control system found in nearly all animals, including mammals, fish, birds, reptiles and invertebrates. This control system is composed of glands (e.g., thyroid, ovary and testis) that produce chemical messengers (hormones) and the receptors in tissues that respond to them.

Generally, the hormones are released into the bloodstream, travel through the body to specific organs, and bind to specific cellular sites called receptors, where they control or regulate key bodily functions and processes including development, growth and reproduction. Any interference with this control system could potentially result in a variety of adverse effects.

Such interference can occur through various mechanisms. For example, some chemicals may mimic a natural hormone and fool the body into over-responding to the stimulus or responding at inappropriate times. Others may block the effects of a hormone. Still others may interfere with the synthesis, transport or metabolism of hormones. Certain drugs, e.g., birth control pills, are designed to intentionally interfere with the normal functioning of specific components of the endocrine system.

EDCs (and potential EDCs) encompass a variety of chemicals, including natural and synthetic hormones (also phyto-estrogens), pesticides, monomers and additives used in the plastics industry, organometals, detergent components and breakdown products, and persistent environmental pollutants like polychlorinated biphenyls (PCBs). These chemicals vary widely in structure and potency. Many of them are persistent in the environment, bioaccumulate through the food chain and are stored in body fat. A number of them have been detected in people and in wildlife, as well as in environmental samples.

Endocrine disruptors have been defined as exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations.

Reasons for concern

In part, concern originated from the finding that some environmental chemicals that are associated with adverse reproductive and developmental effects in wildlife mimic the actions of the female sex hormone, estrogen. In addition, there are indications for an increase in the incidence of some hormonally sensitive cancers, including female breast cancer, and testicular and prostate cancer. Moreover, it is known that prenatal exposure to the potent synthetic estrogen diethylstilbestrol (DES) resulted in adverse reproductive effects and a rare form of vaginal cancer in the daughters of women prescribed this drug to prevent miscarriage.

Fetuses, newborn and developing organisms may be the most susceptible to endocrine disruption, since hormones regulate numerous, specific, normal developmental pathways. Changes in hormone function during critical periods of development could lead to a variety of adverse effects. These effects could be gross or subtle, functional or structural, and many might not be discernible until many years after exposure. Potential effects will vary with the animal species, gender, the dose, and the timing of exposure.

Wildlife

A number of field and laboratory investigations have revealed effects in wildlife populations that may be the result of exposure to EDCs. Such effects have been observed in a broad number of species including mammals, birds, reptiles, fish and invertebrates from North America, Eu-

Abnormalities in the reproductive organs and hormone levels of alligators in a Florida lake probably resulted from a spill of dicofol, a pesticide closely related to DDT.

rope and other continents. The majority of these studies refer to aquatic food chain organisms, and only few to terrestrial systems. The observed effects in various wildlife species include altered sex differentiation with malformed (feminized or masculinized) sex organs, changed sexual behaviour, infertility and impaired immune function.

Impaired reproduction and development have been well documented in a number of species and have resulted in local or regional population changes. However, in many instances the evidence for a causal link with endocrine disruption is weak. The associations found in field studies between the presence of EDCs and reproductive effects have been strengthened by laboratory studies in a number of species. These have demonstrated adverse effects on reproduction and development as well as effects on a variety of endocrine pathways critical to normal growth, development and reproductive function.

High levels of PCBs have been found in the fat of polar bears and may be the cause of the recent striking fall in their fertility.

Although most effects observed in wildlife have been found in heavily polluted areas, there is a potential global problem, as exemplified by the findings of high levels of persistent potential EDCs in certain marine mammals inhabiting oceanic waters. A coordinated, international research programme is needed to assess exposure to and identify the hazards of endocrine disruption to aquatic and terrestrial wildlife.

Humans

The high level of concern for potential adverse effects in humans from exposure to EDCs is based to a large extent on effects observed in wildlife. Some of the effects that are potentially linked to EDCs are listed in the box. However, except for certain exposures at high levels (e.g., to diethylstilbestrol), a causal relationship between exposure to a specific environmental agent and an adverse effect on human health operating via an endocrine disruption mechanism has not been clearly established.

Although it is known that humans are exposed to a number of synthetic chemicals from a variety of sources, information on specific exposures to EDCs is generally lacking. Other factors (e.g., natural hormones, plant hormones), as well as a lack of understanding of endocrine mechanisms of action, also make it difficult to demonstrate a direct link between exposure and effect. There is a need for further research and international cooperation to address these strategies.

IPCS activities

Endocrine disruption issues have attracted widespread attention by the scientific community, the media, national governments and international organizations. The IPCS has taken a leadership role on two projects to address EDC issues globally. In collaboration with national/regional agencies, it has developed a *Global Endocrine Disruptor Research Inventory* of ongoing EDC research, which contains over 700 ongoing research projects from academic, governmental and nongovernmental institutions in over 22 countries.

The IPCS is also preparing a *Global Assessment of the State-of-the-Science of Endocrine Disruptors,* which will be a peer-reviewed, scientific publication emphasizing what is known and what uncertainties remain with respect to the health and ecological effects of EDCs. The assessment will also serve as a basis for fostering internationally coordinated research strategies, and help promote and protect public health and the environment. ◆

Additional information on these projects can be obtained via the IPCS homepage (www.who.int/pcs), the webpage http://endocrine.ei.jrc.it or from Dr Terri Damstra, IPCS (e-mail: damstra@niehs.nih.gov).

Some effects potentially linked to EDCs

- Increased incidence of breast, testicular and prostate cancers
- Decreases in sperm counts and quality
- Increased incidence of defects in the male reproductive tract
- Changes in sex ratio (declining proportion of males)
- Neurological and behavioural disorders in children
- Impaired immune and thyroid function

Poison control in India

A recently established poison centre in Ahmedabad discovers a host of toxic hazards

A Poison Information Centre has recently been set up at the National Institute of Occupational Health (NIOH) in Ahmedabad, India, with the technical support of IPCS's INTOX project. The Centre provides toxicological information to medical personnel, as well as laboratory support for cases of acute or chronic poisoning. Among the cases from the region reported to the Centre, the following, which all involve serious toxic risk, illustrate the great value of establishing poison information centres in developing as well as developed countries.

Toxic solvent misuse

An unlabelled solvent was being used to seal the wrappings for incense sticks. Ingestion of the solvent led to the deaths of six workers from hepatic damage and renal failure. Analysis of the solvent by the Poison Centre showed it to be 1,2-dichloroethane, known to be hepatotoxic, nephrotoxic and a possible human carcinogen. Both workers and employers were informed of the risks to health from exposure to the solvent and were advised to use a non-toxic substitute.

Incorrect label information

Formulations of the pesticide lindane sold in the local market indicated on the label that atropine should be used as an antidote. As a result several people with lindane poisoning were incorrectly treated, their condition worsened and one even died before the intervention of the Poison Centre. The authorities and physicians involved in treating lindane poisoning cases were warned of the faulty labelling and advised to contact the Centre in all cases of pesticide poisoning.

Acute occupational methaemoglobinaemia

Sixteen people had been to the emergency departments of local hospitals, having developed greyish cyanosis and dizziness while washing plastic bags contaminated with dyes and dye intermediates in a canal. The Poison Centre's diagnosis was acute methaemoglobinaemia and all the patients recovered fully following the intravenous administration of methylene blue.

Phorate poisoning among children

Poisoning due to the highly toxic organophosphorus pesticide phorate occurred among 15 school children aged 7-13 years when they were paid to wash empty plastic packings of phorate granules. One child died of respiratory failure and two others needed hospitalization, while others recovered completely. This episode highlighted a worrying lack of awareness and a disregard for regulations concerning the safe disposal of highly hazardous pesticides and their containers.

Indoor spraying of pesticides

The case of poisoning by an organophosphorus pesticide in a hotel worker revealed that pest control agencies often spray agricultural pesticides such as dimethoate and dichlorvos daily inside hotels to control flies, mosquitoes and cockroaches, with blatant disregard of the risks to health.

Unlabelled pesticide powders

Household pesticides are often sold as unlabelled powders or liquids, making it difficult for physicians to diagnose and treat these cases. The NIOH Poison Centre provides routine cholinesterase assays and this helps to differentiate the various types of pesticide poisoning. ◆

Further information about the Ahmedabad Poison Information Centre can be obtained from Dr. A. Dewan, Poison Information Centre, National Institute of Occupational Health, Ahmedabad – 380 016, India (tel: +91-79 286 3751; e-mail: dewan@ad1.vsnl.net.in).

A wealth of information on the Web

As would be expected, the IPCS web site (www.who.int/pcs) contains comprehensive details of all IPCS activities plus lists of all the documents produced. But it does not stop there. The mass of chemical safety information freely available on the site is increasing almost daily. Certain documents are available in their entirety. This applies to the following:

- Over 1000 International Chemical Safety Cards in 8 languages
- Inventory of IPCS and other WHO pesticide evaluations and summary of toxicological evaluations performed by the Joint FAO/WHO Meeting on Pesticide Residues through 1999
- Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (1956-1997)
- Principles of the safety assessment of food additives and contaminants in food (EHC 70)
- Joint FAO/WHO Meeting on Pesticide Residues Reports (1991-1999)

In addition, the summaries of many IPCS publications can be seen on the web site, generally in French and Spanish as well as in English, including:

- all recent Environmental Health Criteria (from no. 200 onwards)
- most of the Concise International Chemical Assessment Documents (CICADs)
- Joint FAO/WHO Expert Committee on Food Additives (JECFA) Reports

Also available on the web site are the requests for data for future JECFA meetings.

Recent publications

Environmental Health Criteria

200 Copper
201 Chloroalkyl ethers, selected
202 Polycyclic aromatic hydrocarbons
203 Chrysotile asbestos
204 Boron
205 Polybrominated dioxins and furans
206 Methyl *tert*-butyl ether
207 Acetone
208 Carbon tetrachloride
209 Flame retardants: tris(chloropropyl) phosphate and tris(chloroethyl) phosphate
210 Principles for the assessment of risks to human health from exposure to chemicals
211 Health effects of interactions arising from tobacco use and exposure to chemical, physical or biological agents
212 Scientific principles and methods for assessing allergic hypersensitization associated with exposure to chemicals
213 Carbon monoxide
215 Vinyl chloride
217 *Bacillus thuringiensis*

Concise International Chemical Assessment Documents

8 Triglycidyl isocyanurate
9 *N*-Phenyl-1-naphthylamine
10 2-Butoxyethanol
11 1,1,1,2-Tetrafluoroethane
12 Manganese and its compounds
13 Triphenyltin compounds
14 Tributyltin oxide
15 1,2-Diaminoethane
17 Butyl benzyl phthalate

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Evaluation of certain food additives and contaminants (forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 884, 1999.

Evaluation of certain veterinary drug residues in food (fiftieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 888, 1999.

Evaluation of certain food additives (fifty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 891, 2000.

Safety evaluation of certain food additives (prepared by the fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives). WHO Food Additives Series, No. 42, 1999.

Toxicological evaluation of certain veterinary drug residues in food (prepared by the fifty- second meeting of the Joint FAO/WHO Expert Committee on Food Additives). WHO Food Additives Series, No. 43, 2000.

Inventory of IPCS and other WHO pesticide evaluations and summary of toxicological evaluations performed by the Joint Meeting on Pesticide Residues through 1999 (WHO/PCS/00.2). Obtainable free of charge from IPCS; also available via the IPCS web site (www.who.int/pcs).

Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (1956-1997). Published on behalf of FAO and WHO by ILSI Press, 1999; freely available via the IPCS web site (www.who.int/pcs).

Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

Pesticide residues in food - 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 148, 1999.

Pesticide residues in food - 1998 evaluations. Part II. Toxicological. World Health Organization, WHO/PCS/99.18, Geneva, 1999.

Unless stated otherwise, these publications are all obtainable from the Office of Marketing and Distribution, World Health Organization, 1211 Geneva 27, Switzerland.

Other publications

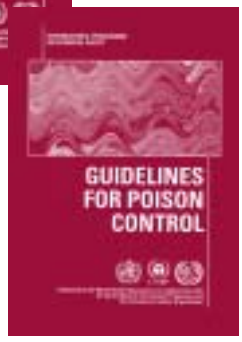
Hazardous chemicals in human and environmental health: a resource book for school, college and university students. World Health Organization, 2000 (WHO/PCS/00.1). Obtainable free of charge from IPCS.

IPCS Training Module No. 3: Chemical risk assessment. World Health Organization, 1999. Obtainable free of charge from IPCS.

IPCS Training Module No. 4: General scientific principles of chemical safety. World Health Organization, 2000. Obtainable free of charge from IPCS.

Public health and chemical incidents: guidance for national and regional policy makers in the public/environmental health roles. 1999. Available from: WHO Collaborating Centre for an International Clearing House for Major Chemical Incidents, University of Wales Institute, Western Avenue, Cardiff CF5 2YB, Wales.

Basic analytical toxicology. World Health Organization, 1995. Now available in English, French and Spanish.



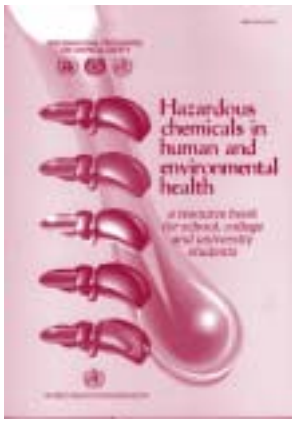
Guidelines for poison control. World Health Organization, 1997. Now available in English, French and Spanish.

Management of poisoning: a handbook for health care workers. World Health Organization, 1997. Now available in English, French and Spanish.

Hazardous Chemicals in Human and Environmental Health

Chemicals have become an indispensable part of our life, sustaining many of our activities, preventing and controlling many diseases and increasing agricultural productivity. The benefits are incalculable, but, on the other hand, chemicals may endanger our health and poison our environment.

Hazardous Chemicals in Human and Environmental Health has been produced by the International Programme on Chemical Safety for the young men and women who will work in industry, agriculture, government and other public or private sectors, so that they carefully consider the potential detrimental effects on health and the environment of hazardous chemicals and take appropriate actions at the local, national or international level for their environmentally sound management. It is hoped that they will leave for their children a better environmental legacy than the one we left for them. ◆



Copies can be obtained free of charge, up to the limit of availability, from the IPCS

Forthcoming publications

Environmental Health Criteria

214 Human exposure assessment

216 Disinfectants and disinfectant by-products

218 Flame retardants: tris(2-butoxyethyl) phosphate, tris(2-ethylhexyl) phosphate and tetrakis(hydroxymethyl) phosphonium salts

219 Fumonisin B_1

220 Dinitro-ortho-cresol

Concise International Chemical Assessment Documents

16 Azodicarbonamide

18 Cumene

19 Phenylhydrazine

20 Mononitrophenols

21 2-Furaldehyde

22 Ethylene glycol (environmental aspects)

Letter from a reader

Pesticide poisoning in the Seychelle Islands

During the 1990s there was a proliferation of uncontrolled importation of pesticides into the Seychelle Islands. There were incidents of large numbers of dead fish in rivers and bays, which were attributed to excessive use of pesticides. There was a steady increase in the number of cases of acute pesticide poisoning through inhalation, skin absorption or ingestion, many occurring among children. The percentage of acute pesticide poisonings among all poisonings rose steadily to 17.6% in 1996, whereas the equivalent rates for the United Kingdom and USA were 5% and 0.6%, respectively. As a primary prevention method, the Seychelles government introduced the Pesticides Control Act in 1996. This regulates the manufacture, distribution, storage, mixing, use and transport of pesticides for the protection of public health and the environment through a multisectoral Pesticides Board. The use of pesticides is now controlled, no organochlorines are permitted, and everyone using pesticides commercially must be trained and registered.

Julita Fostel, Registrar of Pesticides,
Occupational Medicine Unit, Ministry of Health, P.O.Box 52, Mont Fleuri,
Republic of Seychelles

How to obtain IPCS publications rapidly

The fastest way to obtain an IPCS product that has been published by the World Health Organization is as follows. Send your exact mailing address and details of the publication that you require to WHO Distribution and Sales by e-mail (bookorders@who.ch) or fax (+4122 791 4857). Supply details of your credit card, including the card number, expiry date and the card and holder's name. Specify if you come from a developing country since this will permit a reduction in cost.

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