Poisoning by pesticides

The tragic consequence of the unsafe use of pesticides is that the number of deaths from pesticide poisoning has increased over recent years. Many of these deaths occur in agricultural areas of developing countries, where a lack of hygiene, information or adequate controls has created unsafe working conditions, and in small factories where pesticides are manufactured or formulated with little respect for safety requirements.

Accidental poisonings also occur in the home when pesticides are mistaken for soft-drinks or food products, and often it is curious children that are the victims. Then there are the intentional poisonings, where compounds such as arsenic, paraquat, organophosphates and strychnine have been used as suicidal or even homicidal weapons.

Mass poisonings

Mass poisonings are undoubtedly the most dramatic pesticide-related incidents. Several cases have occurred, such as the methyl mercury contamination of seeds in Iraq (over 6000 people affected and over 400 deaths) or the parathion-contaminated flour in Colombia (600 affected and 88 deaths). One of the most recent incidents occurred in Africa in 1991 and involved maize flour treated with endosulfan, an organochlorine pesticide classified as moderately toxic, which had been distributed to farmers as a bait for birds. The flour was mistakenly used to make bread which was eaten by children.

The tragic consequence of the unsafe use of pesticides is that the number of deaths from pesticide poisoning has increased over recent years. Many of these deaths occur in agricultural areas of developing countries, where a lack of hygiene, information or adequate controls has created unsafe working conditions, and in small factories where pesticides are manufactured or formulated with little respect for safety requirements.

Accidental poisonings also occur in the home when pesticides are mistaken for soft-drinks or food products, and often it is curious children that are the victims. Then there are the intentional poisonings, where compounds such as arsenic, paraquat, organophosphates and strychnine have been used as suicidal or even homicidal weapons.

Mass poisonings

Mass poisonings are undoubtedly the most dramatic pesticide-related incidents. Several cases have occurred, such as the methyl mercury contamination of seeds in Iraq (over 6000 people affected and over 400 deaths) or the parathion-contaminated flour in Colombia (600 affected and 88 deaths). One of the most recent incidents occurred in Africa in 1991 and involved maize flour treated with endosulfan, an organochlorine pesticide classified as moderately toxic, which had been distributed to farmers as a bait for birds. The flour was mistakenly used to make bread which was eaten by children.

The tragic consequence of the unsafe use of pesticides is that the number of deaths from pesticide poisoning has increased over recent years. Many of these deaths occur in agricultural areas of developing countries, where a lack of hygiene, information or adequate controls has created unsafe working conditions, and in small factories where pesticides are manufactured or formulated with little respect for safety requirements.

Accidental poisonings also occur in the home when pesticides are mistaken for soft-drinks or food products, and often it is curious children that are the victims. Then there are the intentional poisonings, where compounds such as arsenic, paraquat, organophosphates and strychnine have been used as suicidal or even homicidal weapons.
based on ethanol and methanol.

More than 1400 active ingredients in over 60,000 formulations are in use around the world, but the main pesticides of medical concern are organophosphates (e.g., parathion, diazinon, trichlorfon, mevinphos), carbamates (e.g., aldicarb, propoxur, carbosulfan), organochlorines (e.g., aldrin, chlordane, DDT, ensodulfan), pyrethroids (e.g., cypermethrin, fenvalerate, allethrin), herbicides (e.g., paraquat) and fungicides derived from metallic salts (e.g., mercury and tin). Arsenical salts, although banned in most countries, still represent a threat in places where their use is not strictly controlled. Fumigants, such as cyanide, aluminium phosphate and carbon tetrachloride are extremely toxic, but as they are used only by qualified applicators poisonings are relatively rare.

The management of pesticide poisonings requires not only good treatment facilities but also medical preparedness to deal with possible mass poisonings. It is essential for health personnel to be well trained, diagnostic skills being of prime importance: how to recognize a poisoning, confirm it, assess its severity and indicate the appropriate management.

Although few effective antidotes to pesticides exist, these are usually very valuable, if not essential, for treating poisoning. This applies to atropine and enzyme reactivators (oximes) for poisoning by organophosphates, chelating agents for pesticides based on arsenic, mercury or tin, and to hydroxocobalamine for cyanide poisoning.

IPCS activities in Australia

The involvement of Australia in the activities of the IPCS has increased considerably over recent years. In particular, the Department of Health, Housing and Community Services, in cooperation with other Federal and State Departments of Health and Environment, have successfully organized the funding and hosting of a number of IPCS meetings.

In April 1991, Australia hosted in Adelaide the fourth meeting of the Poisons Centre Working Group for the IPCS Project to develop a poisons information package for developing countries (INTOX), where 56 Poisons Information Monographs were reviewed.

Then in April 1992, an international workshop on the human health and environmental effects of motor vehicle fuels and their exhaust emissions was held in Sydney. The outcome of this workshop was the preparation of documents which will form the basis of Environmental Health Criteria (EHC) monographs on the human health and environmental effects of exhaust emissions from diesel and gasoline engines and from fuels based on ethanol and methanol.

More recently, Australia hosted the IPCS Working Group on methods used to study the neurobehavioural effects of lead in children (Melbourne, October 1992) and the IPCS Task Group on lead (Brisbane, February 1993). Both meetings are important steps in the revision of the 1977 EHC monograph on lead (EHC 3), which is expected to be finalized by late 1993.

Australia is now in the preliminary stages of organizing a workshop on the application of biomarkers in the process of assessing human health and environmental effects from chemical exposures, due to be held in South Australia in October 1993. The purpose of this workshop is to investigate the scientific basis for using biomarkers in risk assessment and to assist the IPCS in the preparation of an EHC document on biomarkers. In addition to its involvement in conducting IPCS meetings, Australia has taken an active role in the drafting of EHC documents. The Department of Health, Housing and Community Services has recently completed a document on amitrole and is currently developing one on chlorodimeform.

IPCS activities

The IPCS has undertaken many activities that will lead to the safe use of pesticides. These include toxicity evaluations and provision of safety information (Environmental Health Criteria, Health and Safety Guides, International Chemical Safety Cards, Pesticide Data Sheets), evaluations of antidote efficacy, a computerized poison information package for developing countries (INTOX), promotion of poison control centres and organization of relevant training courses.

Currently at the planning stage is a project to develop systems for obtaining epidemiological data on acute poisonings, adverse effects and mortality due to pesticides, particularly with respect to occupational exposure. This will provide information on the magnitude of the problem, allow data from the different regions to be compared and highlight areas where additional studies are needed.

The project is being developed by the IPCS with the participation of WHO units such as the Office of Occupational Health and the Divisions of Environmental Health and of Epidemiological and Statistical Methodology. Other UN agencies and non-governmental organizations will also collaborate.
Analytical advice for poisoned patient management

The IPCS/INTOX Project was established in 1988 in order to prepare a computerized poisons information package for poisons information centres and other medical establishments that provide advice on the prevention and treatment of poisoning. One of the outputs of the project is a series of Poisons Information Monographs (PIMs). These give evaluated data needed for diagnosis and patient management including methods of toxicological analysis.

Both simple and complex analytical methods are provided for use under different conditions, e.g., simple methods for hospitals or clinics in developing countries that have no sophisticated equipment, and complex methods that might be used in advanced toxicological laboratories.

Information on tested analytical methods is prepared by experts from various regions of the world, who meet regularly in order to review the proposed methods and prepare advice on the clinical interpretation of the various analytical methods.

The IPCS/INTOX Analytical Toxicology Working Group needs to deal with a wide range of different laboratory techniques in order to cover analytical methods for industrial and household chemicals, various types of drugs, and the variety of poisonous plants that frequently give rise to cases of poisoning. About twenty experts experienced in laboratory analysis for chemicals and in plant identification take part in the IPCS/INTOX Project and during the last few years the Working Group has met regularly in France, Germany, the Netherlands and the United Kingdom.

The most recent meeting, from 7 to 12 November 1992, was hosted by the Algerian Ministry of Health and Population and organized by the Algiers Poisons Centre. Sixteen participants reviewed analytical methods for nine widely used industrial chemicals and pesticides, four drugs, and seven common poisonous plants found in most regions of the world.

This was the first IPCS meeting to have been fully hosted by a developing country, and all the costs were covered by the Algerian authorities as one of their contributions to the IPCS.

Ann Robinson seconded to IPCS

The list of IPCS collaborators grows by the year and one of the most recent additions is Dr Ann Robinson, seconded to the IPCS from the Ontario Ministry of Labour since 1991. She received her original training in non-clinical medicine in London and, after a period lecturing in pharmaceutical chemistry, she became Senior Lecturer in forensic medicine, supervising research with the human distribution of drugs and their metabolites.

Soon after embarking for a new life in Canada, Dr Robinson became Assistant Deputy Minister in the Occupational Health and Safety Division of the Ontario Ministry of Labour, where she was responsible for policy development and programme delivery. This included setting priorities for development of logical project on silica to quantify risk associated with historical exposures in Ontario mines, and was involved in an international project on nickel. She also worked with the Ontario Ministry of Agriculture and Food to determine how the health and safety of workers in the agricultural sector could be improved. In addition, she worked with Labour Canada in examining occupational health and safety issues associated with biotechnology.

Since her secondment to the IPCS, she has worked on such diverse topics as biological markers for toxic end-points in risk assessment, scientific principles for risk assessment, and the assessment of neuro-behavioural effects of lead in children.
Chemicals and the kidney

The kidney is the major organ responsible for maintenance of fluid balance and excretion of water-soluble molecules. Nephrotoxicity is renal disease of dysfunction induced directly or indirectly by chemical and biological agents.

Renal injury by toxic chemicals can manifest itself in different ways, depending on the target site, extent and duration of damage. Toxic nephropathies are not restricted to a single type of renal injury. Some chemicals target specific anatomical regions of the kidney and may affect only one cell type.

The kidney is a target for toxic chemicals because it has a high blood flow, is metabolically active and can generate reactive intermediates, concentrates chemicals and is sensitive to immune reactions. Although the kidney has an effective repair capacity, there are circumstances where damage is irreversible and a series of degenerative changes takes place that sometimes stabilize or else progress to acute or chronic renal failure. The health impact of kidney disease is reflected in the number of cases of renal failure.

Causes

End-stage renal failure is classified on the basis of pathophysiological changes such as glomerulonephritis, pyelonephritis and interstitial nephritis. This gives no indication of cause; infections are obviously important causes but the origin of the majority of cases of renal disease is unknown. The proportion of cases of unknown origin increases with age, but the role of toxic chemicals in the age-related decline in renal function is unknown. Although data are imprecise, nephrotoxicity is a factor in approximately 20% of cases of acute renal failure and around 3-5% of cases of chronic renal failure.

Diagnosis of chemical nephrotoxicity is difficult, although the severity of symptoms and the short interval between exposure and acute renal failure means that there is a better chance of identifying the cause. Most chronic kidney disease has a subtle onset and is not usually diagnosed until a large part of the functional capacity of the kidney has been lost. It is then more difficult to identify the causative agent.

Nephrotoxic chemicals

The kidney may be damaged by a variety of chemicals including therapeutic agents, industrial chemicals, environmental chemicals, and naturally occurring substances. Some chemicals cause acute injury and others produce chronic changes that lead to renal failure.

Therapeutic agents associated with nephrotoxicity include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), halogenated anaesthetics, aminoglycoside and β-lactam antibiotics, lithium salts, cyclosporin A, organometallic compounds (mercury, gold, platinum), radiographic contrast media, cancer chemotherapeutic agents, D-penicillamine, hydralazine, procainamide and diphenylhydantoin. Nephropathies are also caused by metals found in the environment and workplace, e.g., cadmium and lead, and by mycotoxins and other natural toxins.

Risk factors

There are a number of risk factors for the development of nephrotoxicity including genetic predisposition, age, pre-existing renal disease, impaired kidney function, hypertension, diabetes, cardiovascular disease, very high protein diet, and other conditions where there is increased kidney work-load. The combination of chemicals and other disease factors can result in nephrotoxicity, but in this case it can be difficult to define the precise cause.
Balkan endemic nephropathy

Balkan endemic nephropathy (BEN) is a primary chronic non-inflammatory bilateral kidney disease, recognized as a specific clinical entity, affecting only the rural adult population of several Balkan countries. It is encountered in several areas located along the tributaries of the river Danube, but has not, as yet, been identified in other parts of the world. Some of the villages are considered as hyperendemic and others hypoenemic. Although it has certainly been present since the mid-1950s, there are indications that it existed long before.

The disease is, without exception, fatal and therefore causes serious public concern. Its prevalence fluctuates between 0.4 and 10% in various villages, showing a slight decline in recent years, but it has not disappeared from any of the endemic villages. Mortality from BEN ranges between 0.2 and 2.7 per thousand inhabitants. It has been shown that the disease is frequently accompanied by extremely rare malignant urothelial tumours, the prevalence of which is 90 times higher in endemic than in non-endemic areas.

Even a very thorough clinical examination cannot give an unequivocal diagnosis of BEN, since a similar type of kidney impairment is found in various clinical conditions. The initial asymptomatic period is followed by mild intermittent proteinuria, normocytic anaemia and gradually developing creatininaemia. These three signs, together with a positive family history of the illness, are the only ones permitting a diagnosis. Blood pressure is normal and no oedema of nephrotic origin is present.

The cause of the disease is still unknown. Genetic and microbial origins have been ruled out and nephrotoxic heavy metals and drugs are unlikely to be associated with the disease. The most recent hypothesis involves nephrotoxic mycotoxins, in particular ochratoxin A.

Ochratoxin A is a mycotoxin, a secondary metabolite of a variety of moulds, which has pronounced nephrotoxic potency in all species of single-stomached animals so far studied. It is a major disease determinant of porcine nephropathy occurring endemically in several countries.

Ochratoxin A has been found in the endemic region both in human blood, human food and in animal feed samples. However, although it is a recognized nephrotoxic agent and a potential human carcinogen, proof of the association between the disease and this mycotoxin is still lacking and will require a considerable amount of research.

Biological markers

Various biological markers are used for detection of nephrotoxicity. Permanent changes in markers are of greater clinical significance than transient changes. One objective in the use of markers is to recognize tissue-specific damage in the kidney. Most early markers reflect damage to the proximal tubule but do not provide information on damage at the glomerular, distal tubular and interstitial levels. However, the osmolarity of urine may be useful in assessing distal tubular function. There are severe biological markers in urine that help to identify the site of damage. Plasma proteins are normally reabsorbed by proximal tubular cells and only appear in urine due to overflow, competition, kidney dysfunction or damage. The appearance in the urine of serum proteins with a molecular weight in excess of about 50 000 D, such as albumin and transferrin, is an early marker of glomerular damage; β-micro-globulin, α-micro-globulin and retinol-binding protein provide information about glomerular and tubular damage. A permanent increase in high- and low-molecular-weight urinary proteins is an indication of significant renal damage; permanent proteinuria is a reliable marker of degenerative changes in diabetics, patients with Balkan nephropathy (see box) and cadmium nephrotoxicity.

Enzymes as biomarkers

Nephrotoxicity may also be detected by measuring the urinary activity of enzymes released from damaged cells in the kidney. The differential distribution of these enzymes along the nephron can help to identify the site of damage, although this is certainly not precise.

Nephrotoxicity is often immunologically mediated through autoimmune reactions and tests are available to determine the associated immune system changes. Immunochemistry can identify antigens raised to specific components of different segments of the nephron, although it is not possible to determine whether increased antigen excretion results from cell damage, changes in cell turnover rate or other physiological causes.

Other markers have been studied including measurement of prostaglandin excretion, Tamm-Horsfall glycoprotein, and antibodies in urine.

Diagnosis and surveillance

It is still difficult, however, to diagnose accurately cases of chemically induced nephropathies or to predict whether nephrotoxic effects are reversible or progressive. The inability to predict the source of nephrotoxic disease reflects the inadequacies of the methodology available to measure renal injury.
The involvement of China in IPCS activities started in the early 1980s, and in 1987 the Chinese Academy of Preventive Medicine (CAPM), located in Beijing, became the focal point for these activities. The participating institutions, i.e. the Institute of Environmental Health and Engineering and the Institute of Environmental Health Monitoring, form part of the CAPM. A third participating institution, the Institute of Preventive Medicine, is situated in Shanghai Medical University.

The CAPM has been publicizing IPCS activities in ten provinces and a Chinese version of the IPCS brochure will soon be available. The Chinese version of the software for compiling International Chemical Safety Cards has been finalized and 350 cards have now been translated. In addition, 40 selected volumes in the Environmental Health Criteria series have been translated into Chinese.

The CAPM is involved to a large extent in setting national standards for chemicals in air, drinking-water, food and the workplace. It has also established a data base concerning emergency treatment for toxic chemical accidents.

During recent years, the participating institutions have played an important role in the assessment of chemical safety in township industries, the health and socioeconomic impact of chemical pollution in rural industries, and the indoor air pollution resulting from coal combustion which leads to high household levels of fluoride in a few restricted rural areas. In addition, investigations have been made of natural toxins in food, e.g., bangrekic acid in fermented commeal and 3-nitrosopropionic acid in deteriorated sugar cane.

Experts from the Institute of Preventive Medicine have participated in a number of Environmental Health Criteria (EHC) Task Groups and coauthored the EHC document on chlordimeform. In addition, research has proceeded into the health effects of ambient air pollution due to suspended particulates and sulfur dioxide and into the dissemination and use of the WHO Core Test Battery on Behavioural Performance.

Produced jointly by the International Union of Pure and Applied Chemistry (IUPAC) and IPCS, this book is designed as a laboratory reference for scientists, laboratory managers, technicians, environmental officers or teachers working in fields such as chemistry, biology, pathology, clinical biochemistry, chemical engineering and agriculture. Indeed it will be of value to all who need clear guidelines on the procedures necessary to ensure the safe use of chemicals and minimal risk to the general population. The topics covered include protective apparel, safety equipment, first aid, and the storage, distribution and eventual disposal of hazardous chemicals. Available from Cambridge University Press, Cambridge, CB2 2RU, UK.

---

**References**

Mycotoxins and Balkan endemic nephropathy. Food and Chemical Toxicology, 30(3): 117-224.
Forthcoming Meetings

1-3 April 1993
Workshop on International Toxicovigilance: Health Aspects of Chemical Incidents and their Follow-up, Cardiff, Wales

5-8 April 1993
Third meeting of the Working Group on Case Data Harmonization and Collection, Edinburgh, UK

13-16 April 1993
Workshop on Health Aspects of Chemical Accidents, Utrecht, The Netherlands

26-30 April 1993
Peer-review meeting on International Chemical Safety Cards, Geneva, Switzerland

18-22 May 1993
Task Group meeting on Environmental Health Criteria for Amitrole, Toulouse, France

24-25 May 1993
IPCS/CEC meeting on Management of Poisoning Cases: Prevention of Absorption, Milan, Italy

24-28 May 1993
Task Group meeting on Environmental Health Criteria for Hydroquinone, Carshalton, UK

28 June-2 July 1993
Task Group meeting on Environmental Health Criteria for Brominated Diphenylethers, Bromobisphenol A and derivatives, Geneva, Switzerland

2-6 August 1993
Task Group meeting on Environmental Health Criteria for Methyl Bromide, Hanover, Germany

23-27 August 1993
Task Group meeting on Environmental Health Criteria for Glyphosate, Carshalton, UK

20-24 September 1993
Peer-review meeting on International Chemical Safety Cards, Montreal, Canada

20-29 September 1993
1993 Joint FAO/WHO Meeting on Pesticide Residues, Geneva, Switzerland

Recent publications

Environmental Health Criteria

130 Endrin
136 1,1,1-Trichloroethane
137 Electromagnetic fields
138 2-Nitropropane
139 Partially halogenated CFCs (ethane derivatives)
141 Quality management for chemical safety testing
142 Alpha-cypermethrin
143 Methyl ethyl ketone
144 Principles for evaluating the effects of chemicals on the aged population
147 Propachlor

Health and Safety Guides

72 Folpet
73 Rotenone
74 Parathion
75 Methyl parathion
76 1,3-Dichloropropene, 1,2-dichloropropane and mixtures
77 Propachlor

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


Toxicological evaluation of certain food additives and naturally occurring toxicants. WHO Food Additive Series No. 30.

Joint FAO/WHO Meeting on Pesticide Residues (JMPR)


Available from Food and Agricultural Organization, Distribution and Sales Section, Via della Terme di Caracalla, 00100 Rome, Italy.

The open flame from welding and cutting torches can cause the ignition of flammable vapours.

Safety and health in the use of chemicals at work – a training manual, 78 pp, 1993. The aim of this manual, produced by the International Labour Organisation and written in straightforward language, is to ensure that all who come into contact with chemicals know the risks associated with their use and the methods available for reducing them. It provides clear advice on health hazards resulting from chemical exposure at work, chemical fire and explosion hazards, chemical emergency procedures, and the management of a chemical control programme. Available from ILO Publications, International Labour Office, 1211 Geneva 27, Switzerland.

Unless stated otherwise, these publications are obtainable from the Office of Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland. A brochure giving details of all Environmental Health Criteria monographs and a catalogue of reports issued by the Joint FAO/WHO Expert Committee on Food Additives (including an index of substances evaluated by JECFA since 1956) are both obtainable free of charge from the Office of Distribution and Sales.
Countries and national agencies that participate in the IPCS

The following countries and national agencies participate in the work of the IPCS and have expressed their commitment by signing a Memorandum of Understanding.

Countries

Algeria
Australia
Belgium
Brazil
Bulgaria
Canada
Chile
China
Czechoslovakia
Denmark
Finland
France
Germany
Hungary
India
Israel
Italy
Japan
Netherlands
Norway
Poland
Russian
Federation
Sweden
Switzerland
Thailand
Turkey
Ukraine
United Kingdom
Uruguay

Agencies

USA
Agency for Toxic Substances and Disease Registry (ATSDR)
Environmental Protection Agency (EPA)
National Institute of Environmental Health Sciences (NIEHS)
National Institute of Occupational Safety and Health (NIOSH)

China
National Environmental Protection Agency (NEPA).

To our readers:
If you have an article on chemical safety activities that you wish to contribute to IPCS News, please send it to the Editor (the address is given at right).

Forthcoming publications

Environmental Health Criteria
- 140 Polychlorinated biphenyls and terphenyls
- 145 Methyl parathion
- 146 1,3-Dichloropropene, 1,2-dichloropropane and mixtures
- 148 Benomyl
- 149 Carbendazim

Health and Safety Guides
- 78 Methamidophos
- 79 Monocrotophos
- 80 Carbaryl
- 81 Benomyl
- 82 Carbendazim

Joint FAO/WHO Expert Committee on Food Additives (JECFA)
Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series No. 31.

Other publications
International Chemical Safety Cards (CEC/IPCS). Sixth, seventh and eighth series.

CD-ROM
Environmental Health Criteria monographs and International Chemical Safety Cards are now being published and distributed, together with a variety of other key occupational health and safety publications, on a single compact disc labelled OSH Publications. This computer-based information product makes it possible to search, review, cross-reference and print excerpts of these documents in seconds using an IBM-compatible microcomputer. Information about OSH Publications can be obtained from the Canadian Centre for Occupational Health and Safety, 250 Main Street East, Hamilton, Ontario, Canada L8N 1H6.

Summaries in French and Spanish
Readers with French or Spanish as their mother tongue should note that, although EHC monographs are not systematically translated into these two languages, the English version of each monograph carries translations of the Summary chapter into French and Spanish.

Issued by the International Programme on Chemical Safety, World Health Organization, 1211 Geneva 27, Switzerland
Telephone: 7913589  Telefax: 7881949

This newsletter is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale or for use in conjunction with commercial purposes.

The views expressed in this newsletter do not necessarily reflect those of the WHO, the International Labour Organisation or the United Nations Environment Programme.

For a free subscription, please write to the above address.
Editor: Philip Jenkins
Design and production: Marilyn Langfeld
ISSN 1019-0150