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Report of the First meeting of the Global Collaboration for Development of Pesticides for Public Health (GCDPP)

WHO/HQ, Geneva
14-15 October 1998

World Health Organization
Control of Communicable Diseases (CDS)
WHO Pesticide Evaluation Scheme (WHOPES)

INDEX

1. INTRODUCTION

The first meeting of the Global Collaboration for Development of Pesticides for Public Health (GCDPP) was opened by Dr K. Behbehani, Director of the Division of Control of Tropical Diseases, on behalf of the Executive Director of Communicable Diseases (CDS).

Dr Behbehani reiterated the role of the GCDPP as an Advisory Group to the CDS WHO Pesticide Evaluation Scheme (WHOPES) in matters related to the development and safe and proper use of pesticides and application equipment for public health.

Dr Behbehani noted the heavy reliance of disease and pest control programmes on the use of chemicals; the emergence and re-emergence of arthropod-borne infections; further emergence and spread of vector and pest resistance to common pesticides; and safety and environmental concerns over the use of chemicals. He stressed the need for international collaboration and a concerted effort to accelerate the search for alternative pesticides and application methodologies that are safe and more cost-effective, and to advise on the most judicious use of available resources.

Dr M. Zaim, Scientist in charge of the WHO Pesticide Evaluation Scheme (WHOPES), and Secretary of the GCDPP, presented an overview of the WHOPES. He emphasized that safe and environmentally-compatible pesticides continue to be the mainstay of vector-borne disease control in the foreseeable future. He drew attention, however, to the acute need for new control agents/products, if the future success of vector control programmes is not to be jeopardized.

Dr Zaim noted that the GCDPP, by bringing together various partners in the field of public health, would provide a

strong forum for the exchange of technical information and ideas, and would assist WHOPES in planning and providing the highest quality of work towards the development and use of pesticides and application equipment for public health.

The meeting was convened in plenary sessions at WHO/HQ in Geneva 14-15 October 1998, and was attended by 15 representatives of the industrial sector, 10 representatives of national and government agencies, four representatives of Regional and International Organizations, seven representatives of University and research institutions, three WHO Regional Offices as well as members of the Secretariat (see list of participants, Annex 3).

2. SUMMARIES OF THE KEYNOTE PRESENTATIONS TO THE MEETING AND OF SALIENT POINTS IN THE DISCUSSION

2.1 Appropriate pesticides and formulations for vector control programmes

2.1.1 M.S. Mulla. Future requirements for pesticides for vector control – IGRs and biopesticides.

Problems of resistance to many of the synthetic pesticides and concern about their environmental effects, especially in aquatic habitats, has given rise to the need for entirely new classes of agents for the control of vectors larvae. Phytochemicals, microbial agents and insect growth regulators (IGRs) provide a rich source of bioactive substances, from which vector control agents for future use can be developed. To bring these substances into effective use, further systematic laboratory and field evaluation, elucidation of modes of action, development of appropriate formulations and field use patterns, and assessment of safety and environmental risks will be

required. Collaboration between WHO, researchers and industry will be needed to fulfill these requirements.

During the discussion it was pointed out that one of the fields in which IGRs has proved effective in developed countries is in the control of housefly larvae. Recent trials in Pakistan and The Gambia have shown the impact of fly control (by space spraying) on the incidence of diarrhoeal diseases and trachoma, thus demonstrating the importance of new and sustainable means of fly control for disease prevention. Insect growth regulators may well have a role in this respect.

Neem products are used against many agricultural pests and there is increasing interest in various ways of using them against vectors.

2.1.2 C.F. Curtis. Technological developments for impregnation of bednets and requirements for new compounds

Insecticide-treated bednets are receiving renewed emphasis in the Roll Back Malaria Initiative. Permethrin, several different alpha-cyano pyrethroids and etofenprox have all been extensively tested and, in some cases, operationally used for net treatment. There is little to choose between their effectiveness when used at dosages appropriate for each compound. Water-based or tablet formulations are preferable for reasons of safety and convenience. Nets made from polyethylene fibre, into which permethrin has been incorporated at the time of manufacturer, have been tested in various countries and remain insecticidal for at least three years. The threat of pyrethroid resistance has led to the testing of organophosphate and carbamate insecticides (of low toxicity for humans), on bednets in experimental huts in an area where pyrethroid resistance exists in the *An.gambiae* population (see 2.3.2). Higher mortality in both *An. gambiae* and

Culex quinquefasciatus occurred with these nets than with pyrethroid-treated nets.

The need for methods for on-site chemical assay of deposits on nets has been emphasized on a number of occasions. Professor J. Hemingway pointed out that such analysis should be possible using an esterase, which sequesters the insecticide with 1:1 stochiometry. Such an enzyme could be produced in bulk using a cloned gene in a baculovirus expression system. The enzyme is stable at room temperature. Enzyme activity can be assayed with a colour reaction based on alpha- or beta-naphthyl acetate, the colour reaction being readily measurable in the field. The amount of insecticide extracted from a given area of netting would give a proportional reduction in colour production due to its inhibition of the enzyme. At present, the system is only available for certain pyrethroids, however, by site-directed mutagenesis it should be possible to adapt the system to any other pyrethroid.

It was reiterated that, for taxation and customs purposes bednets should not be viewed as a luxury item, but as a means of protecting health.

2.1.3 D. Bernard. Repellents/toxicants for application to skin/fabric for personal protection.

Deet (N,N, diethyl-3-methylbenzamide) is the major active ingredient in 90% of commercial repellent products. An estimated 200 million applications of deet are produced annually and has been the subject of extensive toxicological studies. In 1998, the U.S. Environmental Protection Agency concluded that deet does not cause unreasonable risks to humans or the environment. Deet has the undesirable property of attacking certain plastics. Some other synthetic compounds and plant-based products with proven repellent activity are not plasticizers

and some of them are now on the market. The combination of permethrin-treated clothing and deet applied to the skin has provided 99.9% protection in areas of intense mosquito-biting activity. For reliable assessment of repellents, careful attention should be given to the development of a standardized protocol.

During the discussion, it was emphasized that household insecticides in the form of aerosol cans, vaporising mats, etc. should also be considered as forms of personal protection. These products are of major interest to industry and urban householders in low-income countries who spend considerable sums on these products (e.g. about $2.5 per month per family in several African cities).

2.1.4 A. Sunden-Byléhn. The proposed treaty banning persistent organic pollutants (POPs)

Activities of UNEP were outlined in connection with the proposed treaty, which would include the ban of DDT for anti-malaria use. A data base is being set up to assist countries with information on alternative means of vector control.

During the course of the discussion, the debate in the USA about possible banning of organophosphates was raised. The need for special consideration of public health use of DDT and organophosphates was emphasized. Where alternatives exist, they may require more precautions than DDT to avoid harm to spraymen. Alternatives need to be made affordable to low-income countries and all risks and likely outcomes need to be carefully weighed up to the circumstances in developing countries.

2.2 Quality control of pesticides and application equipment and improvement of application techniques for vector control

2.2.1 G. Matthews. Quality control of pesticide application equipment

According to WHO guidelines (*Equipment for Vector Control, Geneva, World Health Organization, 1990*), indoor residual spraying should be carried out with high-quality compression sprayers equipped with nozzles of appropriate design. However, in many cases, inferior and inappropriate equipment is used, which is likely to waste insecticide by emitting inappropriate droplet sizes and to contaminate the operator through leakage. Blockage of nozzles and filters compromises effective and timely spraying, and may arise from use of cheap equipment which does not meet WHO specifications and/or poor cleaning and storage after completion of work. Spraying is a skilled job for which staff require appropriate "hands-on" training. WHO specifications were published for space treatment equipment but the existing edition does not cover some recent modifications to machinery and smaller equipment suitable for community-based programmes.

The importance of regular re-calibration of equipment and assessment of the spectrum of droplets emitted, was emphasized. The need was pointed out for improved nozzle design to provide for even spraying over a wider range of pump pressures, and for long-throw for more convenient larviciding in marshy areas.

2.2.2 J. Brodesser. Reliability of analytical data – The basis of sound scientific decision

In many countries, there is insufficient quality control of the pesticides which are used. This compromises the

effectiveness of vector control programmes, and is dangerous for operators and for the environment. A survey of agricultural pesticides in use in five countries showed that 25-50% did not comply with FAO specifications. To provide a sound basis for quality control decisions, reliable chemical analytical data are essential. Analytical laboratories should gain accreditation in conformity with the International Standards Organization Guide No. 25, and should participate in regional proficiency testing schemes where sub-samples of a standard material are distributed to many laboratories for testing and the results collected and reviewed by an accreditation authority.

Attention was drawn to the question of the lack of a satisfactory quality control method for *Bacillus thuringiensis* toxin.

2.2.3 V.P. Sharma. Status of insecticide application equipment in the control of malaria and other vector-borne diseases in India

India has some of the largest vector control operations in the world: the targeted population coverage of programmes for malaria, filariasis, visceral leishmaniasis and Japanese encephalitis is respectively 200 million, >100 million, 20-30 million and 10-20 million. Indoor residual spraying is generally carried out with stirrup pumps, not with WHO-specified compression sprayers, and equipment is poorly maintained, with little attention to renewal of nozzles and recalibration of emission rates. The Bureau of Indian Standards has specifications for spraying equipment; however, of the 100 or so manufacturers in India, only 3 or 4 meet those specifications. To try to improve the situation, recent World Bank loans for insecticide have mandatory requirements for resources to renew spraying equipment and protective clothing. Improved training, supervision and management are also required, including

assessment of coverage rates, based on the percentage of rooms and cattle sheds sprayed, rather than on the premises visited.

2.3 INSECTICIDE RESISTANCE PREVENTION AND MANAGEMENT

2.3.1 C.F. Curtis. Resistance management strategies for vector control

It has been suggested that resistance management may be achieved without compromising effective insecticidal vector control by:

a) Limiting insecticide usage to seasons or areas where it is essential, or the choice of those compounds for which the selection pressure for resistance is minimal;

b) Ensuring a dosage is maintained which kills resistant heterozygotes;

c) Alternating the use of different, unrelated compounds, the alternation either being guided by the results of resistance tests, or according to a pre-planned rotation scheme over time, or as a mosaic in space; and

d) Using a mixture of unrelated compounds, each component of which is intended to kill insects that are resistant to the other component.

If resistance genes cause reduced biological fitness, the above-approaches might permanently prevent the emergence of resistance as a serious problem.

The need was emphasized to include in the models the complexity of the ecology of the vector insect, as well as biological factors, such as the effect of irritancy of different

dosages of pyrethroids on the duration of exposure of resistant and susceptible insects. It was also emphasized that, where it is planned to switch insecticides before a resistance gene becomes fixed in the population, there must be an efficient resistance testing system, as was the case, for example, in the Onchocerciasis Control Programme (OCP).

A pre-planned rotation or mosaic strategy for the products of two or more different companies has the commercial advantage of ensuring some demand at all times.

If a synergist can be safely and economically applied to a block resistance mechanism, this may be viewed as a variant of the mixture strategy. Though theoretical models and precedents in the treatment of TB and leprosy favour the mixture method, the extra costs, and the need to test for possible synergistic effects enhancing the hazards to non-target organisms need to be considered.

2.3.2 P. Guillet. The implication of knock-down resistance (*kdr)* development in the use of impregnated bednets

At present, only pyrethroid compounds are used for the impregnation of nets. They have the advantage of low toxicity to humans and high irritancy and insecticide activity on mosquitos. Pyrethroid resistance of the *kdr* type has been detected in *Anopheles gambiae* (Savanna form) in three countries in West Africa. The gene can be detected by a PCR method, and bioassay shows that it causes broad-spectrum cross-resistance to all pyrethroids, as well as to DDT. It is thought that this gene was selected, not by the use of treated nets, but as a result of use of pyrethroids on rice and/or cotton crops. Tests in experimental huts in areas with high or low frequencies of the *kdr* gene show similar mosquito mortality rates in each. The *kdr* gene causes reduced irritability by pyrethroids and it is presumed that free-

flying *kdr* mosquitos therefore tend to remain sufficiently long in contact with the net so that they pick up a lethal dose. A trial in a single village where the *kdr* gene exists showed that insecticidal nets reduced malaria incidence. A larger-scale trial is planned. An Africa-wide network has been set up to test for pyrethroid resistance in malaria vectors not only of the *kdr* type, but also of the other known types, which might cause a serious problem if they co-exist with *kdr*.

2.3.3 J. Hemingway. Resistance monitoring tools and their application to resistance management

In addition to the standardized WHO bioassay system, a suite of methods exists for resistance monitoring by biochemical or molecular tests for the enzymes and genes which underlie resistance phenomena. The methods include colormetric detection of enzyme activities and PCR to amplify, and allow detection of, the genes, which code for the relevant enzymes. These methods make it possible to identify the particular form of resistance which has arisen in a given population. The biochemical/molecular methods can be performed on dead, frozen, or in some cases dry insects, and makes it possible to detect resistance when it is still rare. This is particularly important for genes which are effectively recessive in bioassay, i.e. where only the very rare resistance homozygotes would survive in bioassay, but the much commoner heterozygotes can readily be detected by biochemical/molecular methods. Detection of resistance while the genes are still rare, provides a greater opportunity for setting up rational resistance management systems.

The feasibility of, and the need for funding to set up biochemical/molecular testing facilities in developing countries, was discussed; their use was described in the current trial in

Mexico of rotational and mosaic strategies for resistance management in malaria vectors.

3. CONCLUSIONS AND RECOMMENDATIONS

Although a variety of non-chemical methods of vector control exist and are to be encouraged where appropriate, the fact remains that chemical methods will be the mainstay of vector control in the foreseeable future.

3.1 Larvicidal methods

For certain vector control programmes (e.g. urban malaria and dengue vector control), effective larviciding is the preferred method of control, wherever feasible and cost-effective. At present, synthetic chemicals are the main type of larvicides used for vector control.

3.1.1 Recommendations:

3.1.1.1 Substances of biological origin (such as neem, *Bacillus thuringiensis H-14* and *B. sphaericus)* can play an important role as larvicides, but more attention should be paid to formulations, standardization, quality control and analytical methods.

3.1.1.2 It should not be assumed that products of biological origin are necessarily safe. Toxicological studies and avoidance of dangerous contamination in production and formulation are important.

3.1.1.3 Insect Growth Regulators (IGRs) have been used for insect nuisance control for many years without emergence of resistance or harm to non-target organisms. More opportunities should be sought for their use in vector control in the tropics.

3.1.1.4 The sterilizing effect of IGRs on adult flies should be further investigated.

3.2 Insecticide treated bednets

Insecticide-treated bednets or curtains put an insecticide residue directly in the path of the blood-seeking mosquito and it has now been shown that they are a cost-effective and acceptable means of control of malaria morbidity and/or mortality in several countries.

3.2.1 Recommendations:

3.2.1.1 Individuals and communities should be encouraged to take increased responsibility for the effective use of insecticide-impregnated nets. Education programmes on the use of nets and their re-impregnation should be adapted to the socio-economic circumstances of the particular communities concerned, and appropriate training materials should be prepared.

3.2.1.2 Nets with more prolonged insecticidal effect (e.g. those made from polyethylene fibre which incorporates permethrin) should be further studied to reduce the problem of organizing regular re-dipping of nets. However, the higher cost implications have to be considered.

3.2.1.3 For products formulated for individual dipping of bednets, solid formulations are preferable to sachets because of the high cost of adequately leak-proof sachets

3.2.1.4 Because of the threat of pyrethroid resistance to the continued success of treated bednets or curtains, further testing of non-pyrethroids (such as organophosphates or

carbamates) for treatment of netting should be encouraged. A decision to use such compounds would require rational risk-benefit analysis, taking into account likely exposure during net usage and treatment.

3.2.1.5 Assistance from industry is recommended in development of on-site methods for chemical assay of insecticide deposits on bednets.

3.3 Residual house spraying and space treatments

There is a continuing need for indoor residual spraying against vectors of Chagas disease and many malaria vectors, and for space treatments, for example, in the event of dengue epidemics.

3.3.1 Recommendations:

3.3.1.1 House spraying and space treatments should only be performed by properly trained personnel, wearing appropriate protective clothing and with access to washing facilities.

3.3.1.2 WHO assistance in the provision of well-illustrated training materials in pesticide application methods which are suitable for translation into local vernaculars and adaptation to local conditions should be intensified.

3.3.1.3 Tenders for insecticide should include a reasonable allowance for application equipment and relevant safety equipment, and for spare parts for this equipment.

3.4 Quality Control

There are WHO specifications for pesticides and application equipment to ensure safety and efficacy. The WHO

specifications are part of the International Code of Conduct on the Distribution and Use of Pesticides.

3.4.1 Recommendations:

3.4.1.1 WHOPES-evaluated products, with their data packages, should be linked to the supplier's name as proprietary protection. This implies that the supplier of the same product from a generic source should be required to provide a data set equivalent to that provided by the proprietary company.

3.4.1.2 Clear specifications for packaging and packaging materials should be developed.

3.4.1.3 Labeling should be in accordance with the International Code of Conduct on the Distribution and Use of Pesticides.

3.4.1.4 WHO specifications for pesticide application equipment must be revised to take into consideration new developments, modifications in machinery and requirements for smaller equipment for community vector control.

3.4.1.5 The value of only purchasing equipment which meets the WHO specifications should be re-emphasized to purchasing agents, and spraying equipment for vector control should be chosen according to those specifications, not based on low cost only, as this frequently leads to insecticide wastage and thus a false economy.

3.4.1.6 Application equipment should be properly maintained, regularly recalibrated and characterized for droplet emission.

3.4.1.7 Support to the WHO Collaborating Centres, which provide assistance to governments in quality control of insecticides and application equipment should continue to be given, and strengthened. The analytical laboratories of these centres should be accredited.

3.4.1.8 To ensure that only good quality insecticidal formulations are purchased and used, full specifications of all their components are essential, together with reliable analysis of the content of their active ingredients and formulation characteristics. To ensure such reliability, international networks for cross-checking of analytical competence are to be encouraged.

3.5 Proposals to ban DDT and the debate about organophosphates

An international treaty is being promoted to ban persistent organic pollutants (POPs), including DDT, and the continued use of organophosphates is under debate.

3.5.1 Recommendations:

3.5.1.1 WHO Expert Committees have continued to approve the use of DDT against susceptible malaria and leishmaniasis vector populations for indoor house spraying according to WHO guidelines and specifications. The latter include avoidance of illicit agricultural use. If DDT is to be banned, affordable and effective alternative vector control methods must be available beforehand, and the necessary financial and technical assistance must be provided to the countries concerned.

3.5.1.2 Organophosphate compounds vary widely in their properties. Certain of them are essential for affordable and effective control of vectors of life-threatening vector-borne diseases in tropical countries. The Group was concerned that, in any debate about continued use of any class of insecticide, due weight should be given to its public health usefulness.

3.6 Measures for personal protection from vector-borne diseases

Members of the public should be encouraged to take increased responsibility for their own protection from vector-borne disease. This principle is consistent with initiatives in health delivery systems around the world. In particular, products such as household insecticides and topical repellents should be valuable parts of integrated pest management. This is particularly important in areas where rapid, uncoordinated urbanization has taken place.

3.6.1 Recommendations

3.6.1.1 The use of safe, effective synthetic and natural product-based repellents is recommended to reduce the nuisance of blood-sucking arthropods.

3.6.1.2 Further critical studies on synthetic and natural product-based repellents is recommended, including whether they have a role not only in nuisance abatement but also in disease prevention.

3.6.1.3 National registration and health and trade authorities should co-operate to ensure appropriate cost-benefit and risk-benefit consideration in their countries regarding the supply of new and existing public health and household insecticides, topical repellents and application equipment.

3.6.1.4 Household spraying by consumers should be done with insecticides which are appropriately packaged and labeled for consumer use. Guidelines for safe and effective use of household insecticides should be developed and widely distributed.

3.7 Resistance management

For some vector control programmes resistance has so far not been a problem, for example, triatomine control in Latin America, *Anopheles arabiensis* in southern African after decades of DDT spraying, and nuisance mosquitos in the USA with respect to methoprene. On the other hand, examples of areas where resistance has been detected include DDT resistance in many malaria vector populations, broad spectrum resistance in *Anopheles albimanus* in Central America, temephos resistance in some populations of *Simulium damnosum s.l.*, and pyrethroid resistance in West African *An.gambiae* (Savanna

form). World Health Organization has long supported standardized bioassay methods for detection of resistance and much effort has been devoted to development of biochemical/molecular methods for detection of the mechanisms underlying resistance.

3.7.1 Recommendations

3.7.1.1 Although pyrethroid resistance of the *kdr* type is already a concern in important malaria vectors in some countries, the progress of the use of insecticide treated nets should be continued. However, the impact of bednet programmes on selection for pyrethroid resistance should be investigated.

3.7.1.2 As a basis for putting in place a plan of resistance management, resistance monitoring in malaria vectors should be integrated as an operational component of malaria control programmes. The Group noted that resistance monitoring networks in Africa are promoted by WHO. Such networks should also be implemented in other parts of the world where there are malaria vector control programmes.

3.7.1.3 To choose rationally between the potential resistance management strategies, more needs to be known about the selection pressures for resistance genes when the relevant insecticides are in use and against these genes when the compounds are withdrawn. The extent to which a segment of the target avoids insecticides exposure also needs to be evaluated.

3.7.1.4 As an addition to the well established WHO bioassays, biochemical and molecular methods for monitoring of resistance are recommended because this allows

detection of resistance genes when they are still rare; this is particularly important where resistance is recessive in conventional bioassays.

3.7.1.5 Whether or not detected cases of resistance are having a significant impact on the effectiveness of vector control requires investigation in each case.

ANNEXES

ANNEX 1 WORK PLAN AND FUNDING OF GCDPP

Sub-groups considered the question of funding and the work plan of GCDPP. The following conclusions were presented to the plenary, and the Group agreed to the following:

1. To cover the basic operating costs of the GCDPP, each participant would be encouraged to advance a minimum annual contribution to the GCDPP Trust Fund.

2. The Group agreed to contribute towards activities specified in the recommendations of this meeting. However, it was recognized that outside funding would also have to be sought if all these activities were to be covered.

3. A mechanism was needed for internal communication between GCDPP members, which should be maintained and regularly updated.

4. A survey should be made among the participants of this meeting to determine: (a) their expectations and whether they were met and (b) the target groups of GCDPP and who else should be invited to join.

5. A series of position papers should be prepared on key areas related to the use of pesticides for public health. These position papers should reflect the needs and current levels of scientific knowledge of the different partners within GCDPP.

6. Resources are needed to develop the capability of GCDPP to communicate with internal and external stakeholders who are concerned with insecticides, equipment, consumer products, repellents, vector-borne disease control, etc.

ANNEX 2. AGENDA

Wednesday, 14 October 1998

8.00 – 8.20 Registration

8.20 – 8.30 Opening of the meeting and appointment of officers
Dr Kazem Behbehani, Director, Division of Control of Tropical Diseases

8.30 – 8.40 Chairman's remarks and presentation of the participants

8.40 – 9.00 Overview of the WHO Pesticide Evaluation Scheme (WHOPES) and objectives of the meeting
Dr M. Zaim, CTD/WHOPES

9.00 – 12.30 Appropriate pesticides and formulations for vector control programmes

9.00 - 9.20 Future requirements for pesticides for vector control - IGRs and biopesticides.
Professor M.S. Mulla, University of California, Riverside

9.20 - 9.40 Technological developments for impregnation of bednets and requirements for new compounds
Professor C.F. Curtis, London School of Hygiene & Tropical Medicine

9.40 - 10.00 Repellents/toxicants for application to skin/fabric for personal protection
Dr D. Barnard, USDA, Gainsville

10.00 -10.30 Coffee break

10.30 - 12.00 Discussion

12.00 - 12.30 Draft recommendations

12.30 - 14.00 **Lunch break**

14.00 - 17.30 **Quality control of pesticides and pesticide application equipment and improvement of application techniques for vector control**

14.00 - 14.20 Quality control of pesticide application equipment
Professor G. Matthews, International Pesticide Application Research Centre, UK

14.20 - 14.40 Reliability of analytical data - The basis of sound scientific decision
Dr J.Brodesser, GTZ, Germany

14.40 - 15.30 Status of insecticide application equipment in the control of malaria and other vector-borne diseases in India
Dr V.P. Sharma, Malaria Research Centre, Delhi, India

15.00- 15..30 Discussion

15.30 - 16.00 Coffee break

16.00 - 17.00 Discussion

17.00 - 17.30 Draft recommendations

Thursday, 15 October 1998

8.30 – 15.30	**Insecticide resistance prevention and management**
8.30 - 8.50	Resistance management strategies for vector control Professor C.F. Curtis, London School of Hygiene & Tropical Medicine
8.50 - 9.20	The implications of knock-down resistance (*kdr*) development in the use of impregnated bednets Dr P. Guillet, ORSTOM, Montpellier, France
9.20 - 9.40	Resistance monitoring tools and their application to resistance management Professor J. Hemingway, University of Wales, Cardiff, UK
9.40 - 10.00	Discussion
10.00 - 10.30	Coffee break
10.30 - 12.30	Discussion, continued
12.30 - 14.00	Lunch break
14.00 - 15.00	Discussion, continued
15.00 - 15.30	Draft recommendations
15.30 - 16.00	**Coffee break**
16.00 - 16.45	**Presentation of the recommendations to Dr D.L. Heymann, WHO Executive Director, Communicable Diseases and adoption of the recommendations of the 1st GCDPP meeting**

16.45 - 17.45 **Discussions on the work plan and funding of GCDPP, remarks of the Chairperson and the Secretariat**

17.45 - 18.00 **Closure of the meeting**

ANNEX 3. LIST OF PARTICIPANTS

1. Industry

- Mr I. **Adams**, Reckitt & Colman Products, Scientific Affairs, Asia, Australasia, Cnr Wharf Rd & Hope St. PB.138 West Ryde, NSW 2114, Australia (Tel. 612.9325.4074 - Fax. 612.9857.2001- ian-adams@mail2.reckitt.com.au)
- Dr D. **Coppen**, American Cyanamid, Agricultural Products Division, Chausée de Tirelmont 105, 5030 Gembloux, Belgium (Tel. 3210.494.832 - Fax. 3210.494.833 - coppend@pt.Cyanamid.com)
- Dr S. **Flashinski**, Worldwide Consumer Products, Insect Control R&D, SC Johnson & Son Inc. 1525 Howe Street, Racine, Wisconsin 53403-2236, USA (Tel. 1414.260.3570 - Fax. 1414.260.0216 -)
- Dr G. **Hesse**, Bayer AG, Business Group Animal Health, 51368 Leverkusen, Germany (Tel. 49.2173.38.32.07 - Fax. 49.2173.38.36.84 – gerhard.hesse.gh@bayer-ag.de)
- Mr R.C. **Hudson**, **Jr**., H.D.Hudson Manufacturing Co., 500 North Michigan Ave, Chicago, Illinois 60611-3748, USA (Tel. 1.312.644.2830 - Fax. 1.312.644.7989)
- Dr J. **Invest**, AgrEvo, Environmental Health, 3 Lower Green, Weston Turville, Aylesbury, Bucks HP22 5YU, UK (Tel. 44.1223.252.342 - Fax. 44.1223.252.381 - John.Invest@agrevo.com)
- Dr B. **Jany**, Director of R&D, Clarke Mosquito Control Products, Inc., 159 N. Garden Ave. P.B. 72197, Roselle, IL 60172, USA (Tel. 1-630-894-2000 – Fax. 1-800-832-9344 - clarke@cmosquito.com)
- Dr D. **Kelili**, Technical Expert Euro,DowElanco Europe HQ, Global Business Develop,Buropolis-BP 229, 1240, Route des Dolines-Sophia Antipolis 06904 Cedex, France (Tel. 33-493956000 – Fax. 33-493-956151 - dkelili@wwr.dow.com)
- Mr M. **de Lara**, Curtis DynaFog, 17335 U.S. 31 North, PB. 297-Westfield, Indiana 46074-0297, USA (Tel. 1.317.896.2561 - Fax. 1.317.896.3788 - dynafog@iquest.net)
- Mr Marten **van Maanen**, Development Manager Public Health-Vector Control, Rhône- Poulenc Agro, 14/20 Rue Pierre Baizet, 69009 Lyon, France (Tel. 33.472.85.23.62 - Fax. 33.472.85.27.73- marten.van-maanen@ladargoire.rhone-poulenc.com)

- Dr B. **Martin**, Sumitomo Chemical (UK), Horatio House, 77-85 Fulham Palace Road, London W6 8JA, UK (Tel. 181.600.7700 - Fax. 181.600.7717)
- Mr J. E. **Milliner**, FMC Corporation, International Manager, Speciality Products, 1735 Market Street, Philadelphia PA 19103, USA (Tel. 1.215.299.6471 Fax. 1.215.299.5830 – john_ milliner@fmc.com)
- Dr H. W. **Rauen**, Bayer AG, Agricultural Centre Monheim, Technical Marketing Insect Control, 51368 Leverkusen, Germany (Tel. 49.2173.38.43.33 - Fax.49.2173.38.49.75 – hans-werner.rauen.hr@bayer-ag.de)
- Mr K. **Walcher**, Clarke Engineering Technologies, INC. 159 Garden Ave. PB 72197, Roselle, IL 60172, USA (Tel. 1.630.894.2000 - Fax. 1.630.894.1774 - kwalch@mail.datasys.net)
- Dr G. B. **White**, Vector Control Consultant, Zeneca Public Health, Fernhurst Haslemere, Surrey GU27 3JE, UK (Tel. 44.1428.655.081 - Fax. 44.1428.655.439 - grahambwhite@compuserve.com)

2. National and government supported agencies

- Dr N. **Agui**, National Institute of Infectious Disease, Dept. of Medical Entomology, toyama 1-23-1, Shinjuka-ku, Tokyo-162-8640, Japan (Tel. 81.3.5285.1178 - Fax. 81.3.5285.1150 - agui@nih.go.jp)
- Dr D. **Barnard**, USDA, ARS, CMAVE, 1600/1700 SW 23rd Drive, PB. 14565-Gainsville, Florida 32604, USA (Tel. 352.374.5930 - 352.374.5922 - dbarnard@gainsville.usda.ufl.edu)
- Dr J. **Brodesser**, GTZ, Pesticide Residue Laboratories, Rheinstrasse 91, 64295 Darmstadt, Germany (Fax. 4961.51.898449 - GTZ-da@t-online.de)
- Dr P. **Carnevale**, Institute Pierre Richet, IPR/OCCGE, BP 1500, Bouake 01, Côte d'Ivoire (Tel. 225.63.37.46 - Fax. 225.63.27.38 – Carneval@bouake2.orstom.ci)
- Dr M. **Galoux**, Station de Phytopharmacie, Ministère de l'Agriculture, 11 rue du Bordia, 5030 Gembloux, Belgium (Tel. 3281.625.262 - Fax. 3281.625.272)

- Dr P. **Guillet**, ORSTOM, BP 5045, 34032 Montpellier cedex 1, France (Tel. 33.467 041924 Fax. 33.46754 20 44 - guillet@mpl.orstom.fr)
- Dr J. **Hill**, Malaria Consortium, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK (Tel. 44.151.708.9393- Fax. 44.151.707.1766 - Jhill@liverpool.ac.uk)
- Dr J. B. **Jespersen**, Department of Entomology, Danish Pest Infestation Laboratory, Ministry of Food, Agriculture and Fisheries, Skovbrynet 14, 2800 Lyngby, Denmark (Tel. 45.45.87.8055 - Fax. 45.45.93.1155 - J.B.Jespersen @ ssl.dk)
- Dr G. **Majori**, Istituto Superiore de Sanita, 299 Viale Regina Elena, 00161 Rome, Italy (Tel. 396 49387066 - Fax. 396 49387065 - Majori@iss.it)
- Dr E.N. **Zerba**, Centro de Investigaciones de Plagas e Insecticidas, Zufriategui 4380, 1603 Villa Martelli, Buenos Aires, Argentine (Tel. 541.761.0431/0551 - Fax. 541.709.3210 - cipein@starnet.net.ar)

3. Regional and international organizations

- Ms A. **Sunden-Byléhn**, United Nations Environmental Protection, Chemicals (IRPTC), CP. 356, 15, Chemin des Anémones, CH-1219 Châtelaine (Tel. 41.22.979.91.11 - Fax. 797.34.60 - asunden@unep.ch)
- Dr G. **Matthews**, International Pesticide Application Research Centre, Imperial College at Silwood Park, Buckhurst Road, Sunninghill, Ascot, Berkshire SL5 7PY, UK (Tel. 344.294.234 - Fax. 344.294.339 - g.mattews@ic.ac.uk)
- Dr C.J. **Schofield**, ECLAT, Latin American Network for Research on the Biology and Control of Triatominae, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK (Tel. 44 171 927 2339 - Fax. 44 171 636 8739 - CJ.Schofield@wanadoo.fr)
- Dr M. **Younes**, WHO/International Programme on Chemical Safety (Tel. 4122.791.3574 - Fax. 791.4848 - YounesM@who.ch)

4. Scientists, universities and research institutions

- Dr W.G. **Brogdon**, CDC, Centers for Disease Control, Bldg.102, MS F-22, 4770 Buford Hwy.N.E. Atlanta, GA 30341, USA (Tel. 1.770.488.7750 - Fax. 1.770.488.7794)
- Dr C.F. **Curtis**, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK (Tel. 44 171 927 2339 - Fax. 44 171 636 8739 - c.curtis@lshtm.ac.uk)
- Dr J. **Hemingway**, School of Pure & Applied Biology, University of Wales Cardiff, PB. 915, Cardiff CF1 3TL, UK (Tel. 44 1222 874 621 - Fax. 44 1222 874 305 - SABJH@Cardiff.Ac.UK)
- Professor M.S. **Mulla**, University of California, Department of Entomology, Riverside, 92521-0314 CA, USA (Tel. 1909.787.5818 - Fax. 1909.787.3086- mulla@mail.ucr.edu)
- Dr V.P. **Sharma**, Malaria Research Centre, 20, Madhuban, Vikas Marg, 110092 New Delhi, India (Tel. 9111.224.7983 - Fax. 9111 221.5086 - vps@icmrmrc.ren.nic.in)
- Prof. H. H. **Yap**, Coordinator, Vector Control Research Unit, School of Biological Sciences, University Sains Malaysia, 11800 USM Penang, Malaysia (Tel. 604.657.4776 - Fax. 604.657.7200)

5. Secretariat

5.1. Regional Offices

- Dr L. **Manga**, Regional Advisor, Vector Biology and Control Unit, WHO Regional Office for Africa, Pairenyatwa Hospital, PB. BE 773, Harare, Zimbabwe. (Tel. 263.407.69.51 - Fax. 263.479.01.46 - Mangal@server.whoafr.org)
- Dr H.R. **Rathor**, Regional Advisor, WHO Regional Office for the Eastern Mediterranean, Chemical Safety and Vector Control, PB: 1517, Alexandria 21511, Egypt. (Tel. 203.483.0090/6/7/8 - Fax. 203.483.8916 - RathorH@WHO.SCI.EG)
- Dr G. **Sabatinelli**, Regional Advisor, WHO Regional Office for Europe, 8, Scherfigsvej, 2100 Copenhagen 0, Denmark (Tel. 45.39.17.17.17 - Fax. 45.39.17.18.18 – GUS@who.dk)

5.2. WHO/HQ

- Dr K. **Behbehani**, Director, Division of Control of Tropical Diseases
- Dr B. **Dobrokhotov**, TDR/CME/CPG
- Dr T. **Godal**, Acting Manager, Roll-Back Malaria
- Dr D.L.**Heymann**, Executive Director, Communicable Diseases
- Dr P. **Herath**, CTD/MAL
- Dr M. **Nathan**, CTD/FIL
- Dr M.M. **Younes**, PSC
- Dr M. **Zaim**, CTD/WHOPES

Annex 4.

ABSTRACTS

Future requirements for pesticides for vector control: IGRs and Biopesticides

Professor Mir S. Mulla
University of California, Riverside

Vector control programs around the globe have a critical need for new and effective agents to suppress a variety of disease vectors. In recent years, the number of control agents developed for area-wide control of disease vectors has diminished substantially and few, if any, new control agents reach the stage of commercialization. Due to the emergence of resistance to control agents and environmental concerns, especially in the aquatic and semi-aquatic habitats where a majority of the vectors propagate, most of the early developed control agents have either become ineffective or have been banned by regulatory agencies. We are now at a crucial stage where few effective chemical tools are available for the control of hundreds of species of disease vectors. To meet the urgent need of global vector control programs in the 21st century, it is important to launch needed research programmes on the development of novel, safe and specific control agents, as well as their formulations and proper use.

Phytochemicals, microbial agents and biorational active principles, such as insect growth regulators and others, provide a rich source of bioactive substances from which vector control agents of the future can be developed. The time lag between

finding and identifying a promising control agent and the time when it is employed in control programmes is about 10 years or more. It is therefore highly desirable to establish an ongoing, stage-wise research programme, focusing attention on the development and use of biopesticides (natural products, phytochemical and botanical insecticides and microbial control agents) and insect growth regulators. These groups and classes of pesticides are likely to yield vector control agents of the future. To achieve this important goal, WHO through WHOPES should provide the leadership and organizational scheme to promote collaboration between researchers and industry, with the common goal of finding and developing pesticides of the future that can be used in global vector control programmes. The formation of GCDPP is a step in the right direction and its activities should be supported at all levels.

To launch a research and development programme on IGRs and biopesticides for use in vector control programmes the following research should be initiated and promoted by researchers in academia, research institutions and industry:

1. A systematic laboratory and field evaluation programme on IGRs and biopesticides against important disease vectors.
2. Elucidation of modes of action of new agents affecting various systems and functions in the target vectors.
3. Evaluation and testing tailor-made formulations of use against a variety of target vectors in various habitats and situations
4. Development of field use patterns in disease-endemic areas, transferring knowledge and information to the local vector control programme personnel.
5. Elucidation of the safety and environmental risks of promising new agents, which are likely to reach the field evaluation stage.

In view of the urgent need and demand for safe and effective vector control agents, it is recommended that WHO (WHOPES and GCDPP):

1. develop a comprehensive and ongoing scheme for the development and use of IGRs and biopesticides for vector control;
2. encourage applied research on finding, isolating and evaluating microbial control agents against disease vectors;
3. develop and promote collaboration between researchers and industry to address the problem of lack of wider range of options for the control of disease vectors;
4. act as a lead agency in generating collaboration and cooperation among various segments of academia, vector control entities and the industry;
5. provide and develop uniform protocols for rigorous evaluation of control agents, equipment and formulations.

Technological developments for impregnation of bednets and requirements for new compounds

Professor C.F.Curtis
London School of Hygiene & Tropical Medicine, London, UK

Nearly all the trials of insecticide-treated nets have used one of several different pyrethroids or a near-pyrethroid compound. The alpha-cyano pyrethroids are usable at much lower dosages than is permethrin and appear to be less affected by washing. There seems little to choose between the different alpha-cyano compounds in terms of ability to kill mosquitos, prevent them from feeding or reduce malaria incidence. Water-based formulations are considered safer for those treating nets than are emulsifiable concentrates.

Users of nets freshly treated with some, but not all, alpha-cyano pyrethroids perceive nasal irritation. Tablets of sachets are easy for individuals to use for net treatment, but where treatment is to be done communally, concentrates in 1 litre bottles are cheaper.

Nets made from polyethylene into which permethrin has been incorporated have so far been shown to be effective after 3 years of domestic use and would avoid the need to re-treat annually. Because of the increasing threat of pyrethroid resistance, it is very important to find safe and effective non-pyrethroid compounds for net treatment. So far, an organophosphate and a carbamate (on curtains, not bednets) have been tested in experimental huts; laboratory tests with other classes of compound on netting have not been encouraging, but alternatives are urgently needed.

Repellents/Toxicants for application to skin/fabric for personal protection

Dr D. Barnard
USDA, Gainsville, Florida, USA

Categories of personal protection from biting and disease-transmitting insects include avoidance, physical barriers (e.g., protective clothing) and chemical barriers. Chemical barriers comprise skin-applied repellents and toxicants applied to clothing fabric; repellents and toxicants may be botanical in origin or synthetic. Desirable characteristics for a repellent include efficacy against a broad spectrum of biting insect species, a long protection period, and user acceptability. Desirable characteristics for a fabric treatment toxicant are efficacy, safety, acceptable colour and odour, stability, persistence on fabric, ease of application, and low cost. Botanical products with demonstrated insect-repellent activity

include cedarwood, citronella, geranium, nutmeg, peppermint, and Quwenling (from *Eucalyptus maculata citriodon*).

The synthetic repellent deet (N,N-diethyl-3-methybenzamide) is effective against many species of blood sucking arthropods and is the major active ingredient in 90% of commercial repellent products marketed worldwide. An estimated 200,000,000 applications of deet are made annually. Deet is available in 5% to 100% concentrations and is formulated as solutions, lotions, creams, gels, aerosol and pump sprays, and in towelettes. The pharmaco-toxicology of deet has been studied extensively.

Dermal absorption ranges from 5.6% to 8.4%. High doses of deet administered to laboratory animals have not revealed potential for teratogenicity or oncogenicity in humans. Animal studies show that deet is not a selective neurotoxin, although it can cause irritant contact dermatitis on mucosal membranes. In 1998, the U.S. Environmental Protection Agency (USEPA) concluded that deet does not cause unreasonable risks to humans or the environment but will require revision of product labels to make them protective of users, especially children. Two synthetic repellent compounds 1-(3-cyclohexen-l-ylcarbonyl) piperidine and 1-(3-cyclohexen-l-ylcarbonyl) -2-methyl piperidine are as or more effective than deet against mosquitoes, biting midages, blackflies, ixodid ticks, and mites.

Toxicity studies of these two piperdine repellents are negative, or with no adverse effects; however, an estimated $4 million in additional toxicology tests are needed for USEPA registration, including studies of dermal absorption, chronic teratogenicity and reproduction effects, and chronic dermal toxicity and oncogenicity. Other promising synthetic repellents include ethyl butylacetylaminopropionate and l-methylpropyl 2-(2-hydroxyethyl) -1-piperdinecarboxylate. Treatment of fabric with the pyrethroid permethrin (3-phenoxyphenyl) -methyl (+) cis-trans-3-(2,2-dichloroethenyl) -2,2- dimethyl

cyclopropanecarboxylate) provides a nonstaining, odorless barrier to biting insects that resists degradation by heat and is not removed from fabric, even after repeated launderings. Commonly available formulations of permethrin include 0.5% aerosol and pump sprays. The combination of permethrin-treated clothing and deet applied to the skin has provided 99.9% protection against mosquitos biting human subjects at the rate of 1188 bites/hour.

Future Needs:

1. Identify and develop new repellents for application to skin or fabrics that increase protection against biting arthropods.

   New and effective repellents are needed for use in conjunction with, or as replacements for, deet and for protection from vector-borne diseases, particularly where chemoprophylaxis or immunoprophylaxis for disease is not available or is partially effective. The availability, development, and testing of new repellents need to be coordinated on a global basis.

2. Identify and develop new toxicants for application to fabrics that increase protection against biting arthropods.

   New toxicants are needed to replace permethrin as a fabric treatment. Resistance to permethrin is developing in important vectors worldwide and deet and permethrin used in combination for personal protection may adversely affect health in humans.

3. Develop a standard protocol for the evaluation of efficacy of repellents and fabric-applied toxicants in the laboratory and field.

   Current techniques used to evaluate the efficacy of repellents and fabric treatments, as well as the arthropod

species used in such tests, vary greatly. The implementation of standard testing protocols for laboratory and field evaluations of repellents that incorporates a limited, but globally representative, range of target arthropods would enable meaningful interpretation and integration of repellent test results on a worldwide basis.

Quality control of pesticide application equipment

Professor G. Matthews
Imperial College at Silwood Park, Berkshire, UK

Specifications for equipment used in vector control have been published by WHO to guide users in their choice of sprayers and ensure minimal delays during a control programme due to any breakdown of the equipment. Suitable equipment has been submitted to WHO for independent evaluation both in the laboratory and under field conditions. A series of test rigs are used to determine the durability of sprayers and assess nozzle performance. However, no list of acceptable equipment has been published.

Major manufacturers of this equipment also obtain official registration of their machinery in the country of manufacture. Some manufacturers have a system of marking the equipment that enables the date of manufacture of individual sprayers to be determined, if any fault has been found. Despite these efforts vector control programmes do report problems with equipment. In some cases this is due to purchase of less expensive equipment that was not officially approved, hence the importance of implementing international specifications, but in other cases, equipment has not been properly cleaned before storage or has been stored under inadequate conditions, leading to damage due to corrosion or other causes.

Changes in the control recommendations will require a wider range of equipment to suit the requirements of community-led vector control programme and systems to ensure that appropriate equipment is obtained and properly used. Such systems will involve not only specifications from WHO, but also recognition by health authorities of the need for specialists in equipment and training personnel in vector control.

Reliability of analytical data -The basis of sound scientific decisions

Dr J. Brodesser
GTZ, Darmstadt, Germany

The use of pesticides worldwide is regulated and must be controlled strictly. Physical and chemical properties, production, application, and finally, environmental fate and residue behaviour are comprised in these procedures. In reality, especially in many developing countries, the control of pesticides is incomplete. As a survey on the quality of pesticide formulations worldwide has shown, a huge percentage of imported and reformulated products do not comply with products specifications or with respective national registration. Bad quality products or even those with active ingredients other than as declared, were not the exception, e.g. mosquito coils containing DDT instead of declared synthetic pyrethroids.

Poorly produced products are a waste of funds and much too often they even form obsolete stocks and later hazardous wastes, causing severe environmental and health impacts and exorbitant costs for disposal and site clearance. Therefore, effective control and management of pesticides must be taken into account and given the highest priority. The specific situation of pesticides used for vector control, which is especially relevant for public health, is similar. Promotion and enforcement of the

International Code of Conduct on the Distribution and Use of Pesticides, including the use of WHO specifications, are a suitable and necessary tool to eliminate this nuisance.

To provide a sound basis for further decisions, reliable analytical data are essential, as this will serve as the basis for many subsequent decisions. It is an unequivocal tendency in business and science to improve performance and to ensure the reliability of product quality and data. In industrial research and production, as well as in the scientific fields related to health, agriculture and environment, Quality Management (QM) techniques related to Good Laboratory Practice (GLP) and ISO 9000 series are established to a large extent. The International Standard Organization Guide 25, including linking regulations and documents, is now becoming an issue of emerging importance for servicing laboratories. In this way, QM is dedicated to guaranteeing the quality and reliability of analytical data and at the same time to wining and keeping customer's confidence, not only in the context of international business, but also in science and service.

Accordingly, the implantation of formalized QM measures in analytical laboratories is regarded as being an essential task for the acceptance of laboratories as competent partners. In this regard, for a formal recognition of competence through accreditation along with ISO Guide 25, and in conjunction with the participation in proficiency testing (PT) schemes, it is worthwhile to demonstrate good laboratory performance.

The same applies for setting-up new laboratories. Generally it is insufficient to provide suitable facilities and appropriate equipment if quality assurance measures are not being taken into account as an integral part. Therefore, action to be taken regarding the establishment of specifications and the control of pesticides relevant to public health should be accompanied by measures to ensure quality of data provided.

Consequently, planning and setting up of analytical units should comprise Analytical Quality Assurance (AQA) measures, and participation in PT schemes is a supplementary but unrenounceable part of that. A variety of PT schemes are organized by different institutions, but in many developing countries PT schemes are lacking. This is often a major hindrance preventing participation in interlaboratory comparisons which would be important for gaining recognition and in regard to obtaining formal laboratory accreditation. Interested laboratories often have to adhere to PT schemes organized by institutions situated in developed countries, entailing high costs and forcing laboratories to look for external input abroad. Therefore, in the medium-term, suitable institutions in developing countries should also engage themselves in this field to acquire expertise and to become less dependent on external organizers.

Undertaking independent and anonymous comparisons with other laboratory PT scheme, in conjunction with laboratory accreditation, offers these laboratories the opportunity to provide reliable analytical data. At the same time, it helps customers and authorities to identify competent laboratories. Therefore, adherence to quality management measures is becoming more and more a requirement.

Status of Insecticide Application Equipments in the Control of Malaria and other Vector-Borne Diseases in India

Dr V.P. Sharma
Malaria Research Centre, New Delhi, India

Use of standard insecticide application equipment is critical to success in vector control. Application equipment is procured by the National Malaria Eradication Programme/state health departments/local (self) authorities and other organizations by inviting tenders to select the lowest quotation. Almost all equipment, except motor-mounted fogging machines, is indigenously produced and there are at least 100 manufacturers of such equipment.

Residual insecticides are sprayed using stirrup pumps (double barrel), and in some areas, hand compression sprayers are also in use. Larvicides are sprayed using the knapsack and hand compression sprayers. Portable fogging machines and vehicle-mounted fog generators are used to control active transmission of malaria, dengue, Japanese encephalitis (JE) and mosquito nuisance. The spray operations for malaria control are carried out in about 200 million population each year. In addition, 20 to 30 million of the population require spraying to control kala azar. Japanese encephalitis epidemics are becoming frequent and about 10-20 million of the population require residual spraying and thermal fogging. Larviciding is done in the urban malaria and filariasis control to cover >100 million population. Thermal malathion fogging is becoming popular in towns and industrial establishments to control mosquito nuisance, malaria and dengue outbreaks.

In India, the technical specifications of the equipment are certified by the Bureau of Indian Standards implementing the ISI certification scheme. Manufacturers are given the ISI mark

which is accepted as the approved quality of the product for procurement. There is no other quality control check for equipment used in public health. Studies have shown that the quality of equipment is highly variable. Material used is often substandard and technical specifications do not meet the WHO/ISI specifications barring 3 or 4 manufacturers. Often, equipment is worn out in one year and breakdown is frequent. Equipment replacement is difficult unless it has been used for a stipulated time, and therefore unworthy equipment is used in spraying leading to poor spray.

The flat fan nozzle used in spraying should be pre-tested for its discharge rate of 740-850 ml/mt and replaced every month, which is an exception rather than a rule. The plunger depth of 10-15 cm and 20-26 strokes per minute in the stirrup pump should produce the required spray but in practice, about 40 strokes are required. Spraying should be carried out at a 60 degree angle of the fan maintaining 45 cm distance from the wall, producing swath width of 52.2 cm with 7.5 cm overlapping of each swath. This requires training of spraymen and good supervision, which are often lacking. Maintenance of the equipment is poor and spare parts are not readily available. The particle size of insecticide in the fog should be <25 microns but there are no facilities to ensure proper discharge and particle size. There is great variation in the quality of spraying from state to state and within the state.

Most of these problems are the result of poor perception of the importance of spraying in malaria control. Failure in vector control is often shown due to insecticide resistance. Several studies have revealed that a good spray can still produce epidemiological impact on the transmission of malaria in the so-called resistant and exophilic vector populations. Correct spraying not only produces good impact on transmission but also saves insecticide and reduces environmental contamination.

In order to ensure proper application of insecticides in vector control it is absolutely essential to procure equipment as per the WHO/ISI specifications by introducing rigorous checks on quality and following the norms of nozzle replacement, provision of spare parts for timely repair and proper maintenance of the equipment. Protective clothing, mask, gloves, hood, etc., cholinesterase testing facilities in case of spraying of organophosphorous and carbamate insecticides, should be in place.

Vector control would greatly improve by (i) sensitizing senior programme officials of the critical role of spraying in vector control, (ii) emphasizing the importance of correct and quality spraying in achieving malaria control, (iii) reducing the duration of spray round from 2 1/2 months to 1 month, (iv) spraying should be planned each year as per the local dynamics of malaria transmission, (v) spray equipment should be increased to twice the number at present available in the programme (NMEP) to account for the breakdown and proposed 1 month spray schedule, (vi) use of ceramic nozzle; stainless steel plastic hand compression sprayers, (vii) spray coverage to be targeted for > 90% room coverage and not based on population coverage or house coverage as these are misleading, (viii) clear instructions on the spraying of cattlesheds or otherwise based on the expected outcome in disease vector control, (ix) organizing training programmes on application equipment, its maintenance, spraying technique and norms, and (x) supervision and monitoring of the spray activities from planning to the completion of the spray operations. The real situation on the ground would be discussed pointing out areas requiring improvement.

Resistance management strategies for vector control

Professor C.F. Curtis
London School of Hygiene & Tropical Medicine, London, UK

Resistance management means using insecticide so as to achieve adequate vector/pest control while minimizing the overall selection pressure for resistance genes. These genes tend to cause reduced fitness in the absence of the insecticide concerned and, if the times or places where that insecticide is applied can be sufficiently reduced, it might be possible to ensure that there is no net selection pressure for resistance and thus permanently to conserve the resource of susceptibility genes in wild populations. This might be achieved by:

Limiting insecticide application to the times/places where it is essential for disease control, and/or choice of a method (e.g. insecticide treated bednets) where only the female sex is likely to be exposed to the insecticide.

Maintenance of deposits at a level sufficient to kill resistance heterozygotes, so that insecticide selection only favours rare resistance homozygotes which are likely to be outnumbered in the breeding population by individuals which avoided insecticide exposure. The danger of allowing deposits to decay without timely replacement is that a stage may be reached at which heterozygotes gain a selective advantage over susceptibility homozygotes.

Switching from use of a compound, to which resistance has been detected, to an unrelated compound (for which there is no cross-resistance), and switching back if reversion to susceptibility is detected. This, coupled with switching compounds according to their seasonal suitability, is the basis of the continued successful control of West African onchocerciasis vectors without serious interference from temephos resistance.

A pre-planned rotation of unrelated insecticides or application of them in a mosaic (between the units of which migration can occur). The intention is to maintain a high level of vector control but to ensure that, overall, the selection for any one resistance gene is counterbalanced by natural selection against it. Rotations and mosaics are to be investigated in a field trial on *An.albimanus* in Mexico.

Use of a mixture of unrelated compounds, with intentions similar to method 2, i.e. to ensure that only rare individuals with two resistance genes would gain any selective advantage. Under appropriate conditions this method would be the most effective and it is routinely used with antibiotics. However, there has been a reluctance to test it against insects as it involves investing in doubled quantities of insecticides.

Implications of knock-down resistance (*kdr)* development on the use of impregnated bednets

Dr P. Guillet
ORSTOM, Montpellier, France

Due to some of their properties, pyrethroids are currently the only available insecticides for bednet impregnation. Among these properties, two are of primary importance: KD (knock-down, mosquitos are knocked down before they have time enough to bite) and irritant effects (mosquitos do not spend too much time on treated surfaces and tend to leave rooms fitted with ITMs). An additional important factor is the repellent effect: presence of an ITM in a room significantly reduces penetration of malaria vectors. Repellent, irritant and knock-down effects are among the most important factors determining efficacy of pyrethroid treated nets.

The k*dr* (knock-down resistance) gene, associated with a point mutation on sodium channels of the nervous system, induces a wide range of cross resistance to DDT and to almost all pyrethroids currently available for public health. In the laboratory, resistant mosquitos can survive when exposed at 30 to 40 times higher insecticide doses than susceptible ones. They are no longer susceptible to KD effect and much less susceptible to the irritant one. As a result, resistant mosquitos are able to spend much longer time on treated surfaces and may take advantage of this to take a blood meal through netting or inside a bednet when they found an entry point.

It was recently demonstrated in the field, through experimental hut studies, in resistance areas from West Africa, that *kdr* had fortunately only a limited impact on the efficacy of bednets. Resistant mosquitos were repelled as efficiently as susceptible ones by the presence of permethrin or deltamethrin impregnated nets (same reduction of penetration). Exophilly induced by insecticide as well as repellence (closely related to insecticide concentration), were almost the same whether mosquitos were *kdr* or not. Mortality was also comparable except in the presence of very high insecticide concentrations (1,000 mg/m^2 for permethrin). Although resistant mosquitos could survive in the laboratory at higher concentrations than susceptible ones, they were almost as efficiently killed in the field.

A female mosquito searching for a blood meal from somebody protected by a bednet, spends some time in contact with the netting, searching for a hole or any entry point. In the presence of pyrethroid, this time is very short because of the irritant effect. Protection thus provided is good, even if mosquitos are in fact as much repelled if not more than effectively killed. Since resistant mosquitos have lost their susceptibility due to this irritant effect, they are able to spend much longer time than susceptible ones in contact with treated netting and to pick up by tarsal contact much higher quantity of insecticide. As a result,

observed mortality does not differ that much from susceptible ones.

It was also expected that resistant mosquitos should have some advantages in blood feeding, specially from sleeper's limb in contact with treated netting. This was not the case although in one of the field trials, in Côte d'Ivoire, 25 to 30 % of resistant mosquitos entering huts were able to blood feed versus 10 to 12 % in control area. Finally, rooms fitted with an ITN were no longer suitable as a resting place for malaria vectors whatever they were resistant or not. Since *An. gambiae s.s.* is a very "endophilic" species (resting inside human dwellings), strong exophilly induced by the repellent effect of insecticide results in reduced longevity of mosquitos (flushed out of their normal resting area) and, as a consequence, a lower ability to transmit malaria.

In a bednet trial carried out at village scale in a high resistance area in the Côte d'Ivoire, it was shown that malaria morbidity in children protected by permethrin-treated nets was reduced by more than 50% in comparison with non-protected ones. This protection was in the range of that observed in areas from Africa where mosquitos were susceptible.

Practical conclusions of these studies were that, in experimental huts, resistant mosquitos (*kdr*) have little or no advantage in the presence of an insecticide. When *kdr* is not yet present, it is unlikely this resistance will be selected by the use of ITNs, even at very large scale. In areas where *kdr* is already present, even at high level, ITNs will probably still be effective. Thus, there is no major immediate threat on the use of ITNs even in areas in West Africa where *kdr* is widely distributed.

However, results obtained from experimental huts, although they were very consistent, need to be confirmed at operational level. A large-scale trial should be carried out with the objectives: (1) to confirm efficacy of ITNs in reducing malaria morbidity in

resistance areas; (2) to monitor impact of treatment on the evolution of resistance; and (3), to detect any possible change in the behaviour of malaria vectors.

In addition, impact of resistance on mosquito behaviour may be different if resistance mechanisms other than *kdr* are involved. Furthermore, if several mechanisms are selected within the same population (such as *kdr* plus oxidase-based detoxification), resulting resistance may be much higher than addition of its separate effects. Such synergism has been commonly observed in several insect species, including mosquitos. It is therefore of first importance to settle networks for resistance monitoring among malaria vectors, especially in Africa. Further studies on non *kdr*-based resistance should be strongly encouraged. In case non-*kdr* resistance were detected in the field at significant level, implementation of similar studies in the concerned areas would be highly desirable (it was already detected at low levels in Kenya and the Côte d'Ivoire). Any new pyrethroid showing a different pattern of activity (repellence, irritation, KD) should preferably be tested not only against susceptible mosquitos but also against resistant ones, at least in phases I (laboratory testing) and II (experimental huts).

Despite the encouraging results on the impact of *kdr* (which still need to be confirmed at operational level), risks associated with other resistance mechanisms and their possible interaction with *kdr* should not be under-estimated. As a consequence, the search for alternatives to pyrethroids should remain a key priority for WHOPES.

Resistance monitoring tools and their application to resistance management

Professor J. Hemingway
School of Pure & Applied Biology, University of Wales, Cardiff, UK

Insecticide resistance is an increasing problem faced by those who need to efficiently control medical and veterinary insect pests. In many insects the problem extends to all four commonly-used groups of insecticides. Resistance monitoring programmes should no longer rely on testing the response to one insecticide, with the intention of switching to another chemical when resistance levels rise above the threshold which affects disease control. Effective resistance management depends on early detection of the problem and rapid assimilation of information on the resistant insect population so that rational pesticide choices can be made.

There are now a complete suite of tools for resistance monitoring, which range from simple bioassays, through biochemical assays to PCR-based molecular assays. The utility of the assays in the field depends on the type of control programme being attempted. While the biochemical and molecular assays are more time-consuming (and arguably more expensive) than basic bioassays, they also incorporate a level of extrapolation, for example of cross-resistance patterns between insecticides, which is missing from a bioassay programme.