

42346

EUR/ICP/PCS 017
0803K
ORIGINAL: ENGLISH

**MECHANISMS TO INCREASE
EFFECTIVENESS OF
TOXICITY TESTING IN EUROPE**

Report on a WHO meeting

**Berlin
11-13 December 1991**

1992

EUR/HFA target 19

ABSTRACT

The large and growing number of chemicals in use and an awareness of both chemical pollution and public concern about the possible health effects have led all countries in the WHO European Region to promote action to prevent and control chemical hazards. Because toxicity testing must provide the information needed for such action, the WHO Regional Office for Europe held a consultation to address current problems in such testing and to advise on ways to improve its efficiency. Experts from 15 countries and representatives of three international organizations concerned with toxicology and chemical safety discussed a variety of topics. These included raising the quantity and quality of information derived from toxicity testing, the development of better or alternative procedures (avoiding the use of animals) and the improvement of international cooperation, with special reference to the countries of central and eastern Europe. The participants recommended the regular updating of guidelines on test strategies, a variety of improvements in toxicity testing and test methods (including the use of *in vitro* methods to replace or supplement *in vivo* methods) and ways to improve international cooperation in training, the collection and dissemination of information, and research.

Keywords

TOXICOLOGY
ENVIRONMENTAL MONITORING
ENVIRONMENTAL HEALTH
HAZARDOUS WASTE - prevent/control
EUROPE

CONTENTS

	<i>Page</i>
Introduction	1
Discussion	3
In vivo methods	4
In vitro methods	7
Conclusions and recommendations	9
Annex 1. Working papers	15
Annex 2. Participants	16

Introduction

This could be called the chemical age. About 60 000 chemicals are estimated to be marketed in Europe and 200–1000 new substances are introduced every year. The growth of the chemical industry has been impressive. The output volume is estimated to have doubled every 7 to 8 years throughout the industry's existence, and the amount of chemicals produced per head in Europe has more than doubled each decade.

An awareness of the possible impact of environmental pollution with chemicals and of public anxiety about the possible health effects has led all countries in the WHO European Region to promote action to prevent and control chemical hazards. Because adequate toxicity data are indispensable for the evaluation of chemicals, they are prerequisites for action, including regulatory action, to ensure the safe use of hazardous chemicals. The available data are limited and many chemicals and mixtures of chemicals for which toxicological information is inadequate are still in use.

Information from experiments on laboratory animals alone cannot predict with complete certainty the final outcome for humans of exposure to chemicals. In addition, the interaction of chemicals in the environment cannot be predicted prior to use. The regulation of new chemicals has to rely almost exclusively on toxicological studies conducted before marketing. The additional toxicological information that can become available once a chemical is on the market is therefore of the utmost importance; such information is usually obtained through clinical toxicology or epidemiological studies.

The number of combinations of factors that might influence the health outcomes of exposure to chemicals is so large that the uncertainty from this source can never be entirely eliminated. Assessment before marketing should ideally cover all of the various combinations in all media. In theory, this would mean that the verdict of no observed health effects could not be accepted with certainty until all of these combinations had been examined, which is impossible. Nevertheless, it is essential that a chemical substance be adequately tested prior to mass production. Current experience suggests that most of the chemicals produced in large quantities proceed through about six

years of testing, at a cost of about US \$1 million, prior to their release in Europe. It is important to recognize that, despite all these efforts, some uncertainties can be reduced and some cannot.

In the European Charter on Environment and Health, the governments of Europe adopted the basic principles, mechanisms and priorities for the further development of environmental health programmes. The Charter underlines the importance of international collaboration in environmental health risk management, and calls for the provision of suitable toxicological information to permit effective decision-making at the international and national levels.

Significant efforts are already under way to harmonize toxicity testing at the international level through the application of guidelines from the Organisation for Economic Co-operation and Development (OECD) and mutual acceptance of data and, in the European Community (EC), by the implementation of the sixth and seventh amendments to Council Directive G7/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. The WHO Regional Office for Europe encourages and assists Member States in developing this collaboration through its toxicology programme. This programme will emphasize better coordination through networks of the country authorities that are responsible for safety evaluations of chemicals, and of toxicologists and toxicological institutes. This should promote the efficient use of resources and the harmonization of procedures, reduce the uncertainty about the scientific quality of toxicological studies and introduce better or alternative testing procedures.

The Consultation on Mechanisms to Increase Effectiveness of Toxicity Testing in Europe was organized by the Regional Office with financial support from the German Federal Ministry for the Environment, Nature Conservation and Nuclear Reactor Safety, and hosted by the Federal Health Office in Berlin. The purpose of the Consultation was to address these problems, to advise on mechanisms to improve the quantity and quality of data from toxicity testing and to develop better or alternative testing procedures, avoiding the use of laboratory animals. Moreover, the participants discussed the improvement of international collaboration on toxicity testing, with special reference to the needs of the countries of central and eastern Europe.

The Consultation was attended by experts from 15 countries, representatives of the German Government, OECD and the Commission of the European Communities (CEC), and WHO staff. Professor D. Neubert was elected Chairperson and Dr J. Duffus Rapporteur. The working papers and participants are listed in Annexes 1 and 2, respectively.

Discussion

In recent years, international bodies such as CEC and OECD have achieved considerable success in the harmonization of guidelines and test procedures for toxicity assessment. The establishment of guidelines, however, has had both advantages and disadvantages. The main advantages are:

- the comparability and mutual acceptability of data from different laboratories; and
- the provision of a sound basis for trust between the chemical industry and regulatory authorities.

The main disadvantages include:

- the tendency to adhere to a rigid scheme of testing (called cookbook toxicology), although this is not required by the guidelines; and
- the slowness of procedures to include new scientific evidence in existing guidelines, so that they reflect the current understanding of toxicology.

Agreement has been reached on many test procedures, but toxicological risk assessment should change as science progresses. Test procedures and strategies must be adapted when new information becomes available. Any guidelines have an inherent tendency to fix current procedures and ways of evaluation, and to respond slowly to scientific progress and changing attitudes. Minor or even major changes in test strategies and procedures must therefore be considered regularly; experts from as many countries as possible should take part in this process.

Toxicology is in a period of change. The validity of many procedures used for testing (such as those for carcinogenicity or effects on fertility or the immune system) or for risk assessment are increasingly questioned. Further, the increased concern for animal welfare and new opportunities for *in vitro* methods must now be taken into account. Increased cooperation is thus essential at the levels of both international and national agencies and individual scientists. Optimal risk assessment will result only from extensive cooperation between industry and scientific institutions at universities and other national and international research facilities. One of WHO's goals is to trigger such cooperation in basic research activities.

In attempting to establish new test procedures, three situations can be distinguished. First, an established test procedure may be given a new endpoint (for example, testing for neurotoxicity within the framework of subchronic toxicity testing). In such a case, a new evaluation can easily be included in the established study method. Second, a new method may be considered for an established endpoint (for example, a new short-term test for carcinogenicity). In this case, the new procedure must be shown to equal or surpass other methods. Third, a new method may be considered to replace or complement existing procedures. For example, *in vitro* tests could replace *in vivo* tests for carcinogenicity. This is the most difficult task, since the predictive value of the new procedure has to be evaluated in comparison with that of existing procedures.

Undoubtedly, only extensive international cooperation will enable such changes to be made. Given sufficient coordinated effort, considerable progress may be expected in a number of areas of toxicology.

In vivo methods

Acute toxicity

Two quite different aspects of acute toxicity testing may be distinguished. Information may be needed to label a chemical or to determine its toxic potential (and potency) following a single exposure.

Animal welfare considerations provide one main impetus for the refinement or replacement of current methods. Major problems include the need for clear definitions of toxic classes and for

consensus on endpoints. Death was the classical endpoint and is still used to classify toxicity throughout the world. Nevertheless, there is a trend towards the use of histological, morphological, functional and clinical endpoints. The work of international agencies to harmonize classification systems is to be welcomed and encouraged.

Chronic toxicity (excluding carcinogenicity as an endpoint)

Since the ultimate objective of toxicity testing is to prevent adverse health effects in humans, a risk assessment is usually based on the no-observed-effect level (NOEL) obtained in chronic toxicity studies carried out over 1-2 years. For most chemicals, however, no data are available from such studies. It is therefore important to evaluate the appropriateness of using the data from repeated dose studies) carried out over 28-90 days) as a substitute. This could be done either through the retrospective analysis of chronic and subchronic data or through studies designed specifically for the purpose.

Carcinogenicity

Long-term testing for chemical carcinogenicity is in a special situation, since many substances said to be rodent carcinogens have been detected and the percentage of so-called human carcinogens in the tested substances has exceeded 30% and is approaching 50%. This may be due in part to the inadequacy of the existing test procedure and particularly to the long-term exposure of the animals to extreme doses, which alters their homeostasis. The relevance of such results to humans is therefore uncertain and difficult to interpret. Perhaps a number of tests giving information permitting an understanding of mechanisms of toxicological action may better determine which substances are potential human carcinogens.

Further, the consideration of agents that promote tumours is increasingly important, and testing for tumour promotion cannot be incorporated into classical subchronic testing procedures. Problems arise from the tissue or organ specificity of the agents and the selection of suitable initiators (including the relevant dose to be used).

New strategies need to be worked out for risk extrapolation of carcinogenic toxic agents. This would add quantitative risk assessment

(potency consideration) to classification by strength of evidence, which would assist the setting of appropriate priorities for regulatory action.

Two main areas require development. First, interspecies extrapolation should move away from extrapolation on the basis of dose, for example, mg per kg body weight, to arrive at a target dose estimation by means of physiologically based pharmacokinetics (PBPK). Second, high- and low-dose extrapolation should move away from dose-based mathematical procedures, such as linearized multistage models, and towards biologically driven models, such as the Moolgavka model (MVK). One of the principal problems is the need for a large database, which can only be elaborated for a few substances at present. In addition, the mechanisms of toxic or carcinogenic action must be considered. Finally, the basis for risk extrapolation should be the definition of negligible risk for carcinogenic substances.

Apart from risk extrapolation, strategies should be developed to include elements of risk prediction (such as structure-activity relationships) in the overall process of risk assessment.

Behavioural developmental toxicology

The chemical industry has spent much money in this area, but tests were introduced prematurely and their predictive value is unknown. For this reason, such testing has produced disappointing results, and the usefulness of the present methods and strategies may be questioned. This problem emphasizes the importance of investing in research to establish a good scientific basis for the design and implementation of new test procedures.

The need for behavioural developmental toxicity studies should be reassessed and, if necessary, they should be brought up to an acceptable scientific standard. The refinement of clinical observations and functional tests in perinatal, postnatal and reproduction studies is particularly important.

Respiratory sensitization

Respiratory sensitization is an example of a requirement for a new toxicological method with a new experimental endpoint. Problems

exist in the selection of species, the route of application, the choice of test material (applied unchanged or as a protein-conjugate) and in the selection of immunological and respiratory test parameters.

Immunotoxicity

Immunotoxicity is defined as adverse effects on the immune system apart from sensitization. Research must be carried out to see whether immunological endpoints can be incorporated into the classical procedure for subchronic toxicity. This may be relatively easy for certain (morphological) endpoints, but may not be feasible for others (such as the direct testing of immune functions). Problems may arise in the selection of a suitable species. The rat is the favourite species for general toxicity assessment but does not respond to several well known immunomodulators in the same way as primates. Species differences in many aspects of the immune system remain to be evaluated. Further problems may arise in building a sufficient historical database, and differentiating between direct effects on the immune system and the secondary effects of general toxicity following exposure to a substance with a broad spectrum of effects.

Neurotoxicity

In this context, tests for subchronic toxicity need to be refined to include detailed clinical and functional observations (including vision and hearing) along with detailed histopathology of the central and peripheral nervous systems. The main problems here are the availability of resources such as qualified staff, the selection of adequate reference substances and the differentiation between direct effects and secondary effects resulting from general toxicity.

In vitro methods

Many in vitro methods for toxicological studies have been developed in recent years. Few if any, however, appear to permit the derivation of standard internationally approved test systems for defined toxicological endpoints. On the other hand, in vitro methods may be very useful for screening or obtaining additional information when data

from *in vivo* studies are difficult to interpret. In these respects, *in vitro* tests may even be superior to currently used *in vivo* tests

Assessing the predictive value of *in vitro* tests is one of the main problems with introducing them and incorporating them in present test strategies (except for mutagenicity testing). *In vitro* tests allow only a small part of the mammalian organism to be used, and artefacts must be avoided.

The predictive value of a test must be assessed in several steps. These include:

- assessing variability within and between laboratories;
- testing the outcome with a limited number of substances with well known modes of action; and
- validating the test, which involves the testing of substances with unknown effects in the test system or of pairs of chemically similar substances differing in toxic potential or potency.

Toxicology is a quantitative science and dose-response relationships must be assessed from the *in vitro* data. Further, the data have to be extrapolated to the situation existing in humans, taking account of kinetic variables, and the fundamental science for this must be developed further by research before this will be possible.

Animal welfare is an integral part of laboratory animal science which is concerned with using animals for research in an efficient and humane manner. For the animal, welfare consists of freedom from thirst, malnutrition, chronic discomfort, injury and disease, fear and stress, and the freedom to express natural patterns of behaviour. The last goal cannot be fully achieved in any laboratory study.

Experience and the fundamental similarities in cell structure and biochemistry between animals and humans shows that the laboratory animal model provides a generally valid basis for the prediction of likely effects of chemicals on humans. No animal model, however, is absolutely reliable for such predictions, because of species and strain differences. These must be evaluated and require further research.

Researchers have a legal and ethical responsibility to consider the welfare of the experimental animals in their care. In particular, they must decide whether the use of animals is really necessary in the circumstances. Good animal welfare leads to a better quality of

laboratory animals and thus to better science. Better science in turn will reduce the requirements for animals and give more meaningful results.

Conclusions and Recommendations

1. Changes in guidelines for test strategies and procedures should be considered regularly to ensure that such guidelines accurately reflect the current understanding of toxicology and that new needs for testing are addressed as they appear. International organizations should ensure that experts from as many countries as possible are involved.
2. Testing should follow a staged approach (also known as a step-by-step or tiered approach), in which relatively nonspecific tests are first carried out to determine the presence or absence of effects. The results of these tests should be used to determine whether further testing is necessary. This will ensure that only relevant tests are performed.
3. Test programmes should be considered on a substance-by-substance basis according to the proposed use of each chemical, the likely routes and extent of human exposure and all other relevant information, such as physicochemical properties, structure-activity relationships and information from recorded human exposure. Although guidelines may point out the need for flexibility, researchers have tended to take a "cookbook approach" to their application. More emphasis should be placed on the use of expert judgement to improve and optimize test procedures.
4. In designing test procedures, care should be taken to ensure the welfare of the laboratory animals involved and, where possible and practicable, to reduce the numbers used or even to try to replace in vivo methods with suitable and well validated alternative test systems. Any change in procedure must be carefully checked to ensure that the altered procedures can produce data of an acceptable quality for assessment.

5. The greatest improvement in the assessment of toxicity will come from increasing understanding of fundamental mechanisms, and adequate resources should be directed to the research required.

6. Strategies for the assessment of adverse health effects play a critical role in decisions on which studies are performed on chemicals. Therefore, a scientific approach to the extrapolation of results of experimental studies, including consideration of mechanisms of pathological change, should be encouraged. Such an approach focuses attention on the generation of only the data absolutely essential to decrease uncertainty. This minimizes the number of animals that must be used. Weight of evidence considerations should be applied.

7. Compliance with the principles of good laboratory practice can clearly increase the quality and comparability of toxicity testing. This management tool has the added advantage of ensuring the mutual acceptability of data. Studies forming the basis of risk assessment must also comply with the principles of good laboratory practice. Even studies performed primarily for other purposes benefit from the application of these principles. These should also be used in basic scientific research.

8. In spite of the inherent difficulties of interpretation, human data should be used whenever available, to reduce the need for data from other sources and as a standard to judge the efficacy of both *in vivo* and *in vitro* test procedures. Useful data may be available from poison centres, hospitals, industrial surveillance schemes and studies of the effects of accidents involving exposure to chemicals.

9. Much toxicity data accumulated by industry is not available to further the development of toxicological science. Efforts should be made to provide effective channels to make these data accessible without compromising the confidentiality essential to commercial activities.

10. Validation is urgently needed to assess the predictive value of *in vitro* test systems. It should be performed on a truly representative

selection of chemicals, with adequate consideration of metabolism and relevant biological barriers.

11. Acute toxicity tests *in vivo* are essential for labelling and ensuring the safe use of chemicals. They cannot be replaced at present, but can and should be refined to include more endpoints for assessment. Positive results from validated *in vitro* tests for eye and skin irritation, however, should be sufficient for labelling and administrative requirements.

12. The lack of appropriate data from chronic toxicity studies necessitates the evaluation of the possibility of substituting data from subchronic (repeated dose) tests for the purpose of risk assessment. Existing data should be re-assessed with this in mind, and studies should be undertaken to provide a better basis for quantitative risk assessment.

13. Repeated dose tests should be improved by the inclusion of more detailed clinical and functional observations and detailed histopathology. This will require the provision of resources such as suitably qualified staff, the selection of adequate reference substances, and the development of criteria to differentiate between primary (selective) effects and secondary effects resulting from general toxicity.

14. Increased knowledge of the mechanisms of carcinogenicity is essential to improve the assessment of the potential carcinogenicity of chemicals in humans and should lead to the development of better test systems, both *in vivo* and *in vitro*.

15. In behavioural developmental toxicology, the assessment of behavioural changes should be improved, and the biochemical basis of adverse effects should be established before they are used routinely as test endpoints.

16. Efforts should be made to develop test procedures for respiratory sensitization, recognizing the problems in the selection of appropriate

species, the route of application, the choice of test materials and the selection of test parameters.

17. In testing for immunotoxicity, it may be possible to supplement *in vivo* studies developed from existing repeated dose procedures with validated *in vitro* methods. Such tests do not include pharmacokinetic parameters and their relevance to the *in vivo* situation must be carefully assessed. Care must be taken to distinguish between selective effects on the immune system (primary effects) and general toxic effects (secondary effects). The development of good *in vitro* methods for immunotoxicity testing will require further research; this should be encouraged at both the national and international levels as part of the development of guidelines for test strategies.

18. Special problems arise in the assessment of products of biotechnology and procedures need to be developed for this purpose. The immune responses in test animals preclude long-term studies.

19. The best risk management strategy in the area of health and safety cannot be achieved without major contributions from toxicologists; the other sectors involved should therefore be encouraged to develop better collaboration with and funding of toxicology programmes. This is particularly important in the countries of central and eastern Europe, where the new developments in this area are arising from the efforts of ministries with health responsibilities.

20. Toxicology is a fast developing scientific discipline; in certain areas, knowledge is concentrated in a few laboratories in the European Region. International collaboration should therefore be greatly expanded as it is essential to use all facilities as effectively as possible to meet the ever increasing needs for toxicological knowledge. This collaboration should be developed at various levels and in, for example, training, the dissemination of information, and toxicity testing and other research.

21. International collaboration in training in toxicology may be further developed in five ways. The first is to describe the programmes

and requirements for the degrees in toxicology that can be obtained in several European countries. The International Union of Toxicological Associations (IUTOX) and the European Association of Toxicology (EUROTOX) may be able to help in obtaining this information.

Second, a training course of 1-2 weeks' duration should be organized on special aspects of toxicology such as toxicokinetics, reproductive toxicology, immunotoxicology, animal maintenance and breeding, good laboratory practice, biostatistics, mutagenicity, carcinogenicity and *in vitro* methods. Since such courses are already held in some countries and by some international organizations, they could be extended at a minimal cost to become international courses. Financial support is needed to make such courses available to the international community.

Third, an international programme of fellowships in toxicology should be established for younger scientists. In-depth training for preferably at least two years would allow these scientists to obtain qualifications in the broad area of toxicology. Well trained personnel would help to establish or strengthen research groups and increase the efficacy of existing institutions.

Fourth, a training programme should be established for experienced scientists. They could learn specific methods in toxicology through visits lasting at least two weeks to specialized research laboratories.

Fifth, a programme should be established to support collaboration between experienced scientists and industrial and governmental laboratories. This would enable the scientists to learn procedures essential for the registration of chemical substances and other related research work.

22. The organization of international multicentre studies on particular subjects should be considered, to make optimal use of the facilities available. Such studies would provide a forum for establishing new scientific methods prior to their implementation in regulatory procedures.

23. Broader collaboration between pairs or groups of institutions should be encouraged. This could lead either to the mutual development

of methods and expertise in certain areas of toxicology or to the twinning of institutions for long-term research. The Regional Office for Europe or other organizations could facilitate such collaboration.

24. Specific programmes should be developed to help countries in central and eastern Europe to upgrade their toxicity testing according to their needs and within the framework of basic requirements established by EC and OECD. This can best be achieved through specific projects developed through missions to countries and close collaboration between leading scientists. WHO can play an important role in initiating such projects through its EUROHEALTH programme, which was established to help central and eastern European countries to make reforms in public health.

25. International organizations should establish programmes to strengthen international collaboration in the collection and dissemination of important toxicological information. As soon as possible, the Regional Office for Europe should organize a clearing-house for information on the expertise available in particular research institutions, emphasizing the chances to secure collaboration between the institutions, fellowships and funding for training. Special attention should be paid to matching facilities and funding to existing needs.

Central and eastern European countries should be fully informed of the activities in toxicology and chemical safety already carried out by CEC and OECD. In the context of chemicals control frameworks in central and eastern Europe and the international acceptability of data, OECD should continue its efforts (with the United Nations Economic Commission for Europe and the WHO Regional Office for Europe) to promote the use of test guidelines, the principles of good laboratory practice and compliance monitoring procedures. In addition, international organizations such as CEC, OECD and WHO should organize mini-symposia to discuss new developments in specialized areas of particular importance in toxicology.

26. International organizations such as CEC, OECD and WHO should continue to play their essential role in the further development of international collaboration on toxicology within their respective mandates.

*Annex 1***WORKING PAPERS^a**

- ICP/PCS 017/6 New trends in toxicology and their impact on toxicity testing – scientific/practical aspects, by H.-P. Gelbke
- ICP/PCS 017/7 New trends in toxicology and their impact on toxicity testing – administrative implementation, by G. de Mik
- ICP/PCS 017/8 Implications of animal welfare on toxicity testing – to reduce and redefine the tests, by O. Meyer
- ICP/PCS 017/9 Implications of animal welfare on toxicity testing – to replace the animals, by E.S. Rasmussen
- ICP/PCS 017/10 Benefits of good laboratory practice as a tool to improve toxicity testing, by D. Turnheim

^aCopies may be obtained from the Toxicology and Food Safety unit, WHO Regional Office for Europe, 8 Scherfigsvej, DK 2100 Copenhagen Ø, Denmark.

*Annex 2***PARTICIPANTS***Germany*

Professor Dietlev Kayser

Bundesgesundheitsamt, Abt. CV, Berlin

Professor A. Somogyi

Max van Pettenkofer Institut des Bundesgesundheitsamtes, Berlin

Dr G. Vollmer

Federal Ministry for the Environment, Nature Conservation and Nuclear
Reactor Safety, Bonn

Professor Klaus Wettig

Bundesgesundheitsamt, Abt. CV, Berlin

Temporary Advisers

Dr Vaclav Benes

Chief, Department of Toxicology, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia

Dr Matyas Börzsönyi

Deputy Director-General, National Institute of Hygiene, Budapest, Hungary

Dr Manole Cucu

Director, Institute of Hygiene and Public Health, Bucharest, Romania

Dr John H. Duffus

Director, The Edinburgh Centre for Toxicology, Department of Biological Sciences, Heriot-Watt University, Edinburgh, United Kingdom
(*Rapporteur*)

Dr H.-Peter Gelbke

Abteilungsdirektor, Toxikologie, BASF AG, Ludwigshafen, Germany

Professor Fina P. Kaloyanova

Head, Department of Toxicology, Institute of Hygiene and Occupational Health, Sofia, Bulgaria

-
- Dr Thaly Lakhanisky
Chief, Toxicology Department, Institute of Hygiene and Epidemiology,
Brussels, Belgium
- Professor Nils Gunnar Lindquist
Head, Division of Scientific Documentation and Research, National
Chemicals Inspectorate, Solna, Sweden
- Dr Constantine Loutsidis
National Drug Organization, Athens, Greece
- Dr Constantine Maravelias
Department of Forensic Medicine and Toxicology, University of Athens
School of Medicine, Greece
- Dr R. Maximilien
Life Science Directorate, Department of Pathology and Experimental
Toxicology, French Atomic Commission (CEN-FAR), Fontenay-aux-
Roses, France
- Dr Otto A. Meyer
Head, Biological Section ITA, Institute of Toxicology, National Food
Agency, Søborg, Denmark
- Dr Gerrit de Mik
Director, Substances and Risks Division, National Institute of Public
Health and Environmental Protection, Bilthoven, Netherlands
- Professor Diether Neubert
Institut für Toxikologie und Embryonalpharmakologie der Freien
Universität, Berlin, Germany (*Chairperson*)
- Professor Paolo Preziosi
President, International Union of Toxicology (IUTOX), Chairman,
Department of Pharmacology, Catholic University of Sacred Heart,
Rome, Italy
- Dr Eva Selzer Rasmussen
Senior Research Scientist, Institute of Toxicology, National Food
Agency, Søborg, Denmark
- Dr Kai M. Savolainen
Head, Department of Toxicology, National Public Health Institute,
Kuopio, Finland
- Dr Jan Stetkiewicz
Head, Department of Pathomorphology, Nofer's Institute of Occupa-
tional Medicine, Lodz, Poland

Representatives of Other Organizations

Commission of the European Communities (CEC)

Ms Marie-Thérèse van der Venne

Principal Administrator, Public Health Unit, Health and Safety Directorate, DG V, Luxembourg

Organisation for Economic Co-operation and Development (OECD)

Dr Dian Turnheim

Administrator, Chemicals Division, Environment Directorate, Paris, France

World Health Organization

Regional Office for Europe

Ms Patricia A. Christensen

Programme Assistant, Toxicology and Food Safety

Dr Dinko Kello

Regional Adviser for Toxicology and Food Safety

Dr Maged Younas

Toxicologist, European Centre for Environment and Health, Bilthoven, Netherlands

Headquarters

Dr John Herrman

International Programme on Chemical Safety