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REPORTS

TOXICOLOGY FORUM (18–22 June, 1990 Budapest, Hungary)

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The Toxicology Forum was held June 18–22, 1990 in Budapest, Hungary. Over 160 persons from various countries participated in this international meeting. Poland was represented by Professor Janusz A. Indulski, Institute of Occupational Medicine, Lodz and Professor Teodor Juszkiewicz, Veterinary Research Institute, Pulawy.

The opening ceremony was honored by: *László Surján*, Minister of Welfare, Hungary, *János Szentágothai*, Member of Parliament, Past President and Member of the Hungarian Academy of Sciences, *Clemens Stroetmann*, Secretary of State, Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Federal Republic of Germany, *Philippe Shubik*, President, Toxicology Forum.

Dr P. Shubik gave a brief description of the Toxicology Forum. The Toxicology Forum is a relatively new organization gathering toxicologists who represent basic toxicological sciences, industry and relevant government agencies. An essential purpose of the Forum is to set a stage for an interaction of these three parties as well as for discussions on toxicological problems and exchange of experience. The organisation began in the United States in 1973. Its offices are located in Washington and in London but conferences of the Toxicology Forum are held in different cities. The main objective of the conference organised in Budapest was to discuss the regulation of toxic materials in different areas in the human environment. The Programme Committee consisted of *Dr G. Galvin* (Belgium), *Dr E. Poulsen* (Denmark), *Dr V. Feron* (the Netherlands), *Professor C. L. Galli* (Italy) and *Professor A. Somogyi* (FRG).

Prof. A. Somogyi (Max von Pettenkofer Institute, Bundesgesundheitsamt, FRG) stressed that the regulatory toxicology between East and West was the major driving force that made the meeting happen.

The debates were organised into 8 sessions.

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Session I – East-West Drug Regulations was chaired by *Dr A. Monro* (Pfizer Inc., USA). The EEC drug regulations were presented by *R. Hankin* from EEC. The general drug regulatory framework within the Community is embodied in the so called Treaty of Rome. During the years 1986–87, the single European Act was elaborated which gave the Community the task of achieving by 1992, an internal market, fusing 12 national markets into a single market. In order to accomplish this task all medicinal products present on markets of individual countries within the EEC should be newly authorised and then drug produced in one country could be distributed in other EEC member states: and pharmaceutical companies would not need to go through registration procedure concerning a ready product in each of 12 member states. *R. Hankin* informed that all regulations are published in a series of five volumes which set out the binding Community legislation, a notice to applicants which tells the pharmaceutical industry how to prepare an application for authorization and how to present the results of different tests and trials in a manner which is acceptable now, not only to the 12 EEC member states but, also, to the countries of the EFTA and the Nordic Council and it is increasing being used as a basis for pan-Europe. An application required includes: the summary, the product characteristics, the essential information for the correct usage of product, the description of technology, a technical photography of a product and then expert reports which summarize and comment critically on the development work which has been done during the development of the product, the analytical documentation to guarantee the quality, the preclinical testing and the clinical documentation.

In order to provide the Community with the means to resolve differences between the member states, it is envisaged that there will be established a European Agency for the Evaluation of Medicinal Products (EAEMP) with the task of providing the member states with the best possible scientific advice on the authorisation of new medicinal products.

Tables and Figures demonstrated by *R. Hankin* showed more important details on the EEC activities related to the drug control, cooperation, application forms, required procedures and the structure of the EAEMP.

Professor R.T. O'Neil (Kantonsspital Basel, Switzerland) produced a wide-ranging review of the pharmaceutical regulatory situation in the United States. A schematic diagram of the new drug development process in the United States looks as follows:

1. Pre-clinical research (acute and long-term exposure of animals);
2. Clinical pharmacology studies – Phase I;
3. Controlled studies in patients with the disease or the condition – Phase II;
4. Controlled and open trials – Phase III;
5. Post-marketing surveillance which incorporates combination of spontaneous reports and formal control studies. It provides assessment of the drug safety – Phase IV.

The pre-clinical research is most essential during the course of the

development of the drug and it is the so called investigational new drug application (IND). IND applications are reviewed by the Food and Drug Administration (FDA) within 30 days. Depending upon what the review shows, the drug may be directed for further research, passing all the phases. In the end of Phase II but before Phase III, it is recommended to present to sponsors the summary of all results. Reports on all research and relevant data, listed in the regulation of 1985, are incorporated in the new drug application (NDA) which is submitted to a FDA medical division responsible for that particular drug area. The medical division may ask for additional information. An amended dossier maybe submitted for reconsideration. The amendments are included in a supplement attached to the dossier. The dossier should clearly prove the efficacy and safety of the drug. It is the decision of the FDA whether a new drug is approved or not. At present the FDA is headed by *Dr Robert Temple.* There are various divisions in the Food and Drug Administration which are responsible for particular drug areas. There also is the Office of Drug Standards dealing with drug advertising, epidemiology and biostatistics, and which supplies support to the entire center, both preclinical, clinical and postmarketing surveillance. The investigation staff is responsible for up-dating and reviewing research data included in a drug dossier. It is interesting to note that in 1987, there were additional regulations issued regarding treatment, use and sale of promising investigational drugs to expedite availability to desperately ill patients prior to marketing. This was essentially pushed by the AIDS epidemic in the United States. However, it has also been applied to other life-threatening diseases.

Professor T. Paál (National Institute of Pharmacy, Budapest, Hungary) gave an overview on drug registration and control in Eastern Europe. He stressed that, in general, principles are similar but every country has its own practice as far as new drugs are concerned. Countries of Eastern Europe constitute an organisation called COMECON comprising also Mongolia, Vietnam and Cuba.

Any national drug registration may be characterised by: 1. the requirements to be applied, 2. the guidelines, the use of which is advised when performing pre-clinical and clinical studies, 3. the system which permits marketing of a drug and 4. the regulatory approach, i.e. the practice of application of the former three by the competent authority.

Requirements, a given drug is to satisfy are: quality, safety and efficacy. The quality of the drug is generally assessed by the National Drug Control Institutes.

The next steps are the assessment of the toxicological and experimental pharmacological data. There are guidelines how to perform the research but they are different in individual COMECON countries. Studies performed according to the EEC or US guidelines are not accepted in Poland, Czechoslovakia and Hungary. Guidelines on preclinical and clinical drug investigations meet Western Standards and were issued in a booklet form in Russian.

The regional adverse drug reaction monitoring center, common for all the

COMECON countries, operates in Prague. The center collects side-effect reports. All information is computerized and made available for all cooperating organizations. In 1987 the Compendium Medicamentorum, named COMECON Pharmacopoeia was edited which is comparable to the European Pharmacopoeia but has no legal status. Some countries, such as Czechoslovakia incorporated its several monographs to their national pharmacopoeia. Now, Poland has and Hungary is going to have the observer status in the European Pharmacopoeia Convention. In 1988 the COMECON organization was replaced by international multilateral agreements entered into by individual countries.

Drug registration comprises both pre- and post-marketing phases. Phase I depends on evaluation of drug documentation by expert Committees which usually belong to Health Ministries except Yugoslavia where decisions are taken by the Federal Committee for Labour, Health and Social Security, and Romania where the State Institute for Drug Control and Research has a decisive role. In Hungary, the right of drug registration has been delegated to the National Institute of Pharmacy (NIPh) which operates under the Ministry of Welfare. In Czechoslovakia as a federal country has two independent Health Ministries, two New Drug Committees, two State Institutes for Drug Control and two Import Committees. However, every decision of any of them is binding also for the other Republic (e.g. drug registration, withdrawal from the market, etc.).

In the Soviet Union, Czechoslovakia, Poland and Bulgaria, Drug Committees decide practically about the drug registration, while in Yugoslavia and Hungary they rather play an advisory role. In Hungary, there are four independent drug evaluation Committees: Toxicological, Experimental, Clinical Pharmacological and Clinical.

In Poland the drug registration is granted for an indefinite period, in the Soviet Union for 10 years, in Czechoslovakia and Yugoslavia for 5 years while in Hungary only for 1 year.

In regard to the post-marketing phase, a principle has been operating for two years that every drug needs only one producer for the whole COMECON market. It has already been given up but some of its traces still exist and that is why the drug market is strictly controlled in Eastern Europe.

In Poland and Czechoslovakia, the Drug Control Institutes are also involved in routine drug analytical work, while in Hungary efforts are directed towards registering harmful effects and quality defects. In addition, in Hungary re-assessment system operates which comprises evaluation in the 5th year and in the 15th year after registration. For established drugs (registered abroad) full documentation is not needed in Poland, Czechoslovakia, Yugoslavia and Hungary. In these countries import of non-registered drugs is allowed at a small scale e.g. for life-threatening cases.

To sum up, it can be concluded that differences between Eastern and Western Europe drug registration are smaller than they could be expected.

Sessions II and IV devoted to the regulation of eye and skin irritation testing proved to be very interesting. Nine papers presented during those

sessions dealt with problems related with irritation testing and evaluation of methods.

The session on the regulation of eye irritation testing was chaired by *Dr D.A. Stringer* (ECETOC, Belgium).

Activities of the Commission of the European Communities (CEC) were discussed by *Mrs M.T. Van der Venne* (CEC, Luxembourg). She reviewed methods of eye irritation testing. The review was published by ECETOC in 1988. Interesting results were obtained in the Collaborative Study on 21 chemical compounds. Three groups of tests were performed: chorio-allantoic membrane (CAM), *ex vivo* enuacleated eye and *in vitro* cytotoxicity tests. A good interlaboratory correlation was obtained. The aim of this study was to stimulate thinking on more development or orientation of current efforts allowing to reach international agreement.

Dr. A.P. Walker, UK Consultant, retired after working for many years for Procter and Gamble, in his paper: *Scientific critique of Draize test*, presented the assessment and his comments on this test employed in the studies of the eye irritation by chemical substances. He indicated similarities and differences between the Draize test and Friedenwald, Hughes and Hermann tests previously used. Then he discussed such questions as: selection of species for the study, the maximum volume of material tested, the volume of test material instilled into the rabbit eye which could be used to predict potential irritation of the human eye, effect on cornea, iris and conjunctivae, classification of toxic effect of chemicals by means of the Draize test. In summary, *Dr Walker* suggests that the Draize rabbit eye test, using a test volume of 0.1 ml of the chemical substance, would appear to give a reasonable grading of chemicals as potential eye irritants, providing that the chemicals or preparations are not surface-active. But the evidence supports the assertion that the effects of these types of products on the human eye are best predicted by a test volume of 0.01 ml or its multiplication.

Dr M. York, a toxicologist, previously involved in the detergents industry, now works at the research etablishment of Unilever, UK. He is responsible for performing skin and mucous membrane irritation studies using detergents in personal care products, interested specifically in skin and eye testing for pathology. In his paper: *A new approach: Research into new methods, Dr York* presented a wide range of new methods which can replace the Draize test in eye irritation test. A range of approaches to *in vitro* eye testing may be classified within various categories which embrace methods based on physicochemical properties, microbiological tests, cytotoxicity, tissue cultures, *in vitro* corneal injury test using enucleated rabbit eyes. *Dr York* stated that none of the presented methods of eye irritation *in vitro* reliably replaces the *in vivo* eye test. There is no general legislative approval for *in vitro* tests, particularly in the area of hazard classification, although in some cases, authorities are willing to accept *in vitro* data which identifies materials as hazardous.

Dr P.A. Botham (ICI Central Toxicology Laboratory, UK), after listening to papers presented during the session on the regulation of eye irritating testing, made some critical comments on the assessment of irritation in

industry recommended by ECETOC and compared it with the modified techniques used now by EEC and OECD. According to *Dr Botham* animal tests should be eliminated as much as it is possible, particular criteria should be applied when chemicals of low or high pH are considered, data from well-validated alternative tests should be used to indicate whether a given chemical substance is a severe irritant or corrosive, more use should be made of observations on the application of local anesthetics to reduce pain in the eye caused by chemicals.

Finally, *Dr Botham* stressed that the recommendations of the ECETOC Task Force were that there should be an international harmonization of methods, that three animals, as shown in the EEC and OECD 1987 guidelines, are sufficient, that the human approach to testing should be optimized by means of stepwise procedures and possibly, also, the use of low-volume studies, *in vitro* alternative testing procedures should be applied, that other information derived from studies should be used, especially from Clinics of Occupational Diseases and European Poison Control Centers, and that the results should be very carefully interpreted in regard to humans.

Session IV chaired by *Dr G. Calvin* (Procter and Gamble European Technical, Belgium) was focused on skin irritation testing.

Mrs M.T. Van der Venne (Commission of the European Communities, Luxembourg) presented CEC views on irritation testing. The Council Directive 86/609/EEC puts stress on animal protection used in experiments, recommended the re-assessment of toxicological methods and encouraged international experts to use alternative methods to reduce pain and suffering in animals. It is essential now to accept *in vitro* studies aiming at the replacing of animals in experiments. It was also suggested that *in vitro* studies could be used in the complex of pre-screening toxicological studies in order to identify irritating chemicals especially when a large series of unknown compounds have to be considered. These were, however, suggestions arising from small scale studies which have to be confirmed and approved before international regulations be submitted for final approval.

Professor C. Galli (University of Milan, Italy) has been for many years concerned with research on *in vivo* skin irritation methodology and on cell culture. He spoke on scientific criticism on skin irritation test which included the following controversial data: single dose, subjectivity of grading, no quantitative data, mechanism of toxicity, reversibility of effects, species differences. If alternative tests, based on a purely scientific ground, are validated one should not always refer to Draize results, at least because we know that rabbit skin is different from human skin. Nevertheless, the end points *in vitro* and *in vivo* are more or less the same. They can be looked at in view of morphological changes, cell demages, metabolic processes, mitosis, hyperplasia or proliferation, necrosis or cell viability.

Closing his presentation, *Professor Galli* expressed his views on ECETOC guidelines on studies which should embrace: collection of information, preliminary screen (*in vitro*), secondary screen (*in vivo*), single exposures, repeated exposures, studies in man with special reference to using available information

in the assessment of irritation. The preliminary screen is very important however, it is insufficient and a battery of screens should be considered, in order to save animals and avoid, at the same time, the single exposure before making studies on man.

Dr M. Pemberton (Imperial Clinical Industries Chemicals and Polymers Ltd., UK) used to work in the Central Toxicology Laboratory where he was concerned with matters of mechanisms of skin and eye irritation. In his presentation: *An industry assessment and recommendation for future action*, he tried to answer the following questions: What is the purpose of irritation testing? What is skin irritation in man? Under what circumstances does dermatitis occur? How should irritation or corrosion be assessed (method based upon Draize test)?

Dr Pemberton stated that the use of all sources of information is essential for toxicologists to make better assessment of true hazard in man. The ECETOC Task Force groups these sources of information into five categories: paper assessments, *in vitro* assessments, *in vivo* assessments in animals (single exposure), *in vivo* assessments in animals (repeated exposure), studies in man (clinical and epidemiological).

Dr M. Martens (Monsanto Company in Brusseles, Belgium), in his paper: *Alternative approaches*, discussed the possible *in vivo* alternatives to the EEC/OECD primary skin irritation test in the rabbit listing advantages and disadvantages of the EEC/OECD test.

The advantages are: the important historical database, the rabbit is an easy animal to handle, a large skin surface available, and most widely used skin irritation method. The disadvantages of this testing method can be subdivided into two categories: the considerable inter-laboratory variation of results, and species differences in skin response. The optimal technique of reading of the effects is extremely important, however, one technique is insufficient and only employment of a number of testing methods can produce reliable results.

Mr C. Stroetmann (Secretary of State, Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, FRG) was the chairman of the session on the regulations of chemicals. In the key-note speech he stressed that these regulations are indispensable. It is a task for scientists, industries, authorities and politicians to make the handling of the stuffs safer, especially having in mind that the number of only old ones is more than 100,000. This issue can be solved through the international cooperation. An important role in this direction have organizations like EC or OECD. Cooperation between East and West is also necessary. The regulation of chemicals needs worldwide standards and it is assigned for the safety culture in industrialized society.

Dr G. del Bino (Commission of the European Communities, Brussels, Belgium) overviewed the EEC dangerous substances directive. He said that on 18 September, 1979 the EC Council adopted the sixth amendment on dangerous substances. The member states were required to implement it by 18 September 1981. Until the end of 1989, 788 full notification dossiers had been submitted in the community for new chemical substances placed on the market in quantities greater than 1 tonne per annum. For substances manufactured

outside the community, the directive forsees that a notification dossier should be submitted for each direct import. This means that for the same substance may be many repeated notifications. For substances placed on the community market in quantities less than one tonne per annum, the manufacturer must submit a limited announcement to the authorities. It is forseen that the Commission will publish by the end of 1990 a list of all new substances. At the moment, the European official list of dangerous substances with their formally agreed classification contains 1 200 entries. This figure will increase to around 1 600 by the end of 1990.

Article 2 of the sixth amendment forsees the possibility to classify substances as dangerous for the environment. But, until now, no criteria were available to enable such a classification to be made.

The proposal for the seventh amendment to directive was adopted by the Commission in January 1990 and it is now the subject of discussion in the Council. This amendment is intended to rectify any weaknesses and anomalies which have come to light during the 9 years of practical experience in the implementation of the sixth amendment. However, it will retain the same philosophy as the 6th amendment and it will be rather modification and not revision.

The most important changes are: harmonized notification for substances marketed at less than one tonne per annum; identification of the legal representative of manufacturers outside the community; avoidance of duplicative animal testing; definition of the symbol "dangerous for the environment", and risk assessment of new chemicals.

Mr G.S. Hassing (Procter and Gamble, European Technical Center in Belgium) gave an industry overview on the regulations of chemicals in Europe. He stated that the sixth amendment to the EC Council directive has been a starting point in the development of regulations on chemicals in Europe. Nevertheless, there are areas where certain modifications are required, e.g., real requirements for risk assessment should be identified, some of the methods of toxicity assessment should be updated, the procedure by which human data can be used should be clearly defined, the so-called "dangerous for the environment" substances should be more clearly classified.

Dr J.E. Brydon (Organisation for Economic Co-operation and Development, Paris, France) touched on a number of aspects of the OECD work dealing with new chemicals. Within OECD there are 24 countries, plus Yugoslavia and the European Commission. Since 1970 the OECD has developed its concern about the impact of economic development on environmental degradation and vice versa and the impact of environmental protection regulations on economic development. The work on monitoring of pesticides in the environment led to the formation of the Group on Unintended Occurrence of Chemicals in the Environment. The Group started its activity with studies of three problems of polychlorinated biphenylene (PCB), cadmium and mercury. At present, the main objectives of the organization is better harmonization of instruments needed to support broad-based approaches to chemical control. The OECD goals are as follows: to improve the protection of

health and the environment from the harmful effects of chemicals; to avoid distortions of trade in chemicals; to reduce the economic and administrative burden on the member states associated with chemical control; to foster intensive international exchange of information on chemicals. The OECD accomplishment which deserves a special stress is the so-called "MAD" decision (Mutual Acceptance of Data) taken in 1981. It says that data generated in the testing of chemicals in an OECD member country, in accordance with OECD test guidelines and OECD principles of good laboratory practice, shall be accepted in other member countries for purposes of assessment and other uses (pesticides, drugs, etc.). Right now the OECD guidelines for testing of chemicals are being updated and modified.

Bearing in mind international accomplishments, the following international instruments for the management of chemicals, used by the OECD and other organizations should be mentioned:

1. Agreements:
   - Conventions and associated protocols,
   - Agreements (e.g. on 30% reduction of SO_2),
   - OECD Council decisions.
2. Official recommendations supporting harmonization and standardization;
3. Unofficial recommendations:
   Non-governmental organizations,
   Scientific bodies.
4. Technical instruments leading to the law harmonization: principles, guidelines, criteria documents, reports e.g. ECETOC, WHO.

The existing chemicals programme comprises the following objectives:

1. the identification, from the 100,000 existing chemicals, of the most important ones of concern for health and the environment;
2. the development of an information base (data and interpretation) on those chemicals so that the level of concern can be established;
3. the management and control of those (toxic or hazardous) chemicals of significant or major concern.

The OECD has a data base, called IXCHEM with 6 000 chemical entries. This work is going on in the member countries, so that, in that sense IXCHEM could be considered a gross priority list of chemicals of concern.

Professor J.A. Indulski (Institute of Occupational Medicine, Lodz, Poland) discussed the present regulation of chemicals in Poland.

In Poland there is no homogeneous legal body of acts determining the limits of chemicals in different environmental media and defining, at the same time, effective regulatory controls for the protection of human and environmental health. There is a variety of rules and regulations of different rank, ranging from general statements in the Polish Constitution to executive acts issued by administrative bodies.

In the structure of state administration the major body is the State Sanitary Inspectorate which collaborates with other institutions like the State Labour Inspectorate, the Environmental Protection Inspectorate, the Radiolo-

gical Protection Inspectorate, and so forth. Among legal regulations, the following ones are most important: Law on health conditions of food and nutrition, Labour Code, Law on the environmental protection, Law on the nuclear power, Law on the state sanitary inspection and other regulations regarding land development, building, conservation of inland waters and the Code of Misdemeanours.

Administration at the national, regional and local levels is responsible for control whether regulations are followed and obeyed. At the central level, Minister of Environmental Protection and Natural Resources coordinates all ectivities. The mandatory regulations define MAC values for chemicals in the environment at working posts, in the air of dwellings, in the air and water as well as the indirect evidence of adverse health effects of the environment.

In Poland there are 27 regions covering several per cent of the total area and inhabited by 35% of the population where levels of contamination continue to exceed admissible norms. Four of the regions have been regarded as areas of ecological disaster. At present, there are no studies which could indicate a direct relationship between the exposure of the general populations and adverse health effects.

In order to initiate and coordinate actions intended to limit the human and environment exposure to chemicals, the Chemical Safety Project in Poland has been worked out. The Project is based on research, information, risk assessment and risk management. The Project has been received with great interest and it is expected that the National Coordinating Committee for Chemical Safety be called into being in the near future.

Issues discussed during Session VIII on consumer products regulation was closely related with Session V. The Session was chaired by *Dr David Clark* (Unilever Research and Engineering, UK). Four papers were presented.

Directive 88/379/EEC: Classification, packaging and labelling of dangerous preparations was presented by *Mr G. Mosselmans* (Commission of the European Communities, Belgium). The first community directive concerning dangerous substances, regarding classification and labeling of dangerous substances was issued in 1967. New directives followed in 1973 and in 1977. These three directives created the ground for Directive 88/379/EEC which is now mandatory.

Through the inventory it is known that there are around 100,000 chemicals and around 800,000 preparations on the European market.

Mr Mosselmans indicated insufficient number of good laboratories for testing all substances and preparations.

The directive says that testing of substances and preparations is based on tests of general use and that the producer or the importer is responsible for the procedure. They are obliged to label properly substances and preparations to give information for the protection of the user. The physical and chemical properties, clinical effects, single exposure toxicity, repeated exposure toxicity, irritant and corrosive effects, carcinogenic, mutagenic and teratogenic effects are taken into consideration in the classification of chemical toxicity. Safety data sheets are being now introduced for each substance as a kind of information addressed to users.

Dr V. Scailteur (Procter and Gamble, European Technical Center, Belgium) presented the industry comments on Directive 88/379/EEC. She indicated that not all substances and preparations are labeled. In her opinion activities should be harmonized to provide all substances and preparations with appropriate labels. Depending on the kind of risk, each substance should be marked in a relevant way. The substance is characterised on the basis of physical and chemical properties (these are usually substances which explode easily, oxidizers, and combustible substances), and toxicological properties (very toxic, toxic, dangerous, irritative and corrosive).

Dr P. Kovář (Fat Industry, Prague, Czechoslovakia) spoke about consumer product regulation from the Czechoslovakian point of view. He stated that in Czechoslovakia production continue to grow and that consumption of various products becomes still greater. This is related with growing pollution of the environment mainly water and air. Pollution in turn, produces irreversible changes in living organisms. In order to prevent the environment against further degradation it is essential to use sewage-treatment plants, where biodegradation methods, based on bacterial cultures, are used. The efficacy of sewage-treatment plants should be controlled by means of testing methods recommended by the International Standard Organization (ISO).

Session VI – Food additives and pesticide residues – was chaired by *Mr Emil Poulsen* from the Danish Ministry of Health. Four presentations were given during the Session.

Professor J. Kagan, (All-Union Scientific Research Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastic, USSR) presented criteria of assessment and classification of pesticides according to their toxicity and hazard degree. High biological activity of pesticides, progressing expansion of their application in many countries, their ability to accumulate in biological and water-food chains, their penetration into a man's organism with food-stuffs of plant and animal origin produce adverse health effects in the majority of the world population. An international system dealing with toxicology of pesticides should be set up to assist in solving the problem. This would require a large-scale exchange of information, access to methodological and hygienic recommendations adopted in individual countries, and to criteria of assessment and classification of pesticides, assessment of toxicity and hazard degree. The identification of a lethal dose and exposure level are indispensable in the essessment of toxicity.

The danger of toxic substances for a man is defined, to a great extent, by their ability to accumulate. Therefore study of cumulation is a necessary requirement for hygienic regulation of pesticides. A quantitative assessment of the substance cumulative properties is one of the major criterion of toxicological studies. Definition of harmful effect of the substance, non-effective doses and concentrations should be the subject of experimental studies. Acute, sub-acute and chronic toxicity should be investigated. Biochemical and immunological studies deserve special attention. Effect of pesticides on the enzymatic system of monooxigenase (MOGS) is very important in the hygienic evaluation. Blastomogenic properties are also detected in experimental animals. A significant bulk of data on oncogenic properties of pesticides is available

in the monograph of the International Agency for Research in Cancer (IARC, 1972–1985).

Mutagenic effects of pesticides are discussed in the monograph of Kurinny and Pilinskaya (1976).

Data of embryotoxic and teratogenic properties of some pesticides also draw attention to. Studies of delayed effects of exposure are of great importance but very difficult. In the future, assessment of the relationship between effects, dose and duration of chemical exposure as well as comparison of data, obtained on experimental animals, with observations on people and wide epidemiological investigations will be imperative.

In 1968, the Hygienic Evaluation of New Pesticides was made in USSR (Medved, Kagan, Spynu). In 1987 some amendements were introduced to the hygienic classification reflected in the third edition of the Methodological Instructions for Hygienic Evaluation of New Pesticides.

Dr Hallas-Møller (Commission of the European Communities, Belgium) in his paper: *Food additives: Situation in EEC*, gave an overview on the present EEC situation in regard to food additives. The first EEC list of food additives was issued in 1962 in the directive on colouring matters.

Later followed directives on preservatives (1963) antioxidants (1970), emulsifiers, stabilizers, thickening and gelling agents (1974).

It was decided to issue a directive how to use food additives authorized in all the EEC member states. An article in the directive lays down that "provisions that may have effect upon public health be adopted after consultation with the Scientific Committee for Food (SCF)", established in 1974. Since 1986, there have been 17 ordinary members in SCF and there have been appointed 4 emeritus councellors. The Committee, whose term lasts three years, meets in plenary sessions 5–6 times a year. Working groups have been also established for different subjects such as additives, contaminants, packaging materials, etc. For the SCF plenary sessions experts in various areas are invited. The opinions of the Scientific Committee for Food are published in reports by the Commission. So far 23 report series have been published and 2 others are in press. The main topic of reports has been food additives but a number of other topics has been also discussed such as free monomers and additive for packaging materials, composition of food for infants and young children, food irridiation, solvents and a few contaminats. SCF has been established as an advisory body for the European Communities. The EC together with SCF and EEC member states published Guidelines for presentation of data on food additives. These guidelines set out the format of an application and outline which information should be supplied: full chemical description including impurities, description of manufacture together with methods of detecting it in food, information on possible degradation and reaction products when used in foods, justification for its use in food as well as assessment of food samples. The toxicological data show the safety of the substance and its intended use shall comprise studies on mutagenicity, chronic and subacute toxicity, carcinogenity, teratogenecity and embriotoxicity. All other data are published in original reports. The full dossier shall be available in microfilms/fiche copy.

The intention of SCF is to set out guidelines for all food additives. Recently, the use of sweeteners instead of sugar has considerably increased. Therefore, an official proposal on aweeteners for use in foodstuffs will be published soon with reference to the acceptable daily intake (ADI).

Dr J.A. Moore (Institute for Evaluating Health Risks, USA) presented the US view on pesticide regulations.

Within the United States there is one law that deals with pesticides. It is the Federal Insecticide, Fungicide and Rodenticide Act. Collection of data on efficacy, stability active ingredients, chemical form, environmental and human health hazards, acute and sub-acute toxicity are major elements evaluated for registration. The hygienic evaluation of pesticides residues in food is comprised in the Federal Food, Drug and Cosmetic Act (FFDCA). The expanded system of analysis of pesticides residues in foodstuffs is named the Dietary Residue Evaluation System (DRES). The USDA data is a basis for DRES operation. In the United States there are roughly 300 pesticides for use in foods. A considerable number of pesticides was registered already 30 years ago. In 1988 the US Congress adopted the law on reregistration of all pesticides used in the United States.

Dr D. Arnold, (Bundesgesundheitsamt, FRG) chaired Session VII on veterinary drug regulations. He indicated that many countries have taken measures to control the use of veterinary drugs. From the early beginning veterinary drug residues in food of animal origin have been a persistent public health concern. For this reason, the establishment of an FAO-WHO Codex Alimentarius Committee for Residues of Veterinary Drugs in Foods is of great importance. It is the internationally recognised forum for solving food safety issues and providing all consumers around the world with the same high level of protection from potentially harmful residues.

Another area where harmonization is urgently needed is the veterinary drug registration itself. The International Technical Consultation on Veterinary Drug Registration (ITCVDR) in cooperation with the International Office of Epizootics (IOE) is responsible for these issues and it is considered the appropriate platform for representatives from the national registration authorities from all over the world.

Dr L.M. Crawford (US Department of Agriculture, Washington D.C.) shared his experience on the control of chemical residues in food in the US. Studies of safety food as a preventive measure, have been carried out for only 25 years. Meantime a number of national and international institutions has been established. All of them try to coordinate their activities.

The establishment of standards of sanitary regulations for agricultural products is of great importance. Codex Alimentarius (CODEX), the International Office of Epizootics (IOE) and the International Plant Protection Convention (IPPC) cooperate in this area.

The United States has long worked closely with the CODEX. This is an organization that standardizes international food regulations and develops internationally agreed-upon maximum residue limits in food. It also pays much attention to acurate registration of veterinary drugs. The Committee on Residues of Veterinary Drugs in Food has been set up to provide a stable

fundation for international egreement on sanitary and health measures that protect consumers and promote fair trade. Every year the Committee completes the list of ingredients which is the subject of studies. On the initiative of President Bush, a comprehensive food safety plan was proposed to protect consumers from danger posed by pesticide chemicals and to provide safety food. This plan enhances the authority of the US federal government in taking preventive measures.

They comprise amongst others the establishment of scientifically sound threshold tolerance levels for pesticides in food, increasing the penalties for misuse of pesticides, control and collection of information on the distribution, use and testing of pesticide products.

The President's Food Safety Plan reflects the cooperation of experts representing this institution with the Environmental Protection Agency (EPA) which registers pesticides and sets the legal limits for pesticides in food. FDA regulates all foods other than meat for safety and finally USDA regulates meat and poultry.

Activities of the Commision of the European Communities were discussed by *Dr R. Hankin* (Directorate General for Agriculture, Brussels, Belgium). The Directorate General for Agriculture is responsible for legal processes of authorization, control and monitoring of veterinary drug residues. The regulation of veterinary medicines is very similar to that in relation to human medicines. The main directives were adopted by the European Communities in 1981. They dealt with governing the procedures for authorization and testing of veterinary medicines. In 1987 new directives, dealing specifically with products derived from biotechnology, were issued. At the present time, there are a number of important amendments to these directives which are currently under discussion.

The Committee for Veterinary Medicinal Products (CVMP) has been established to ensure coordinated application of testing requirements of regulatory control to individual products. The Committee brings together representatives of the 12 member states. The CVMP working groups deal with specific aspects of control of veterinary medicines, technical standards for immunological veterinary medicines and hormones for zootechnical or therapeutic purposes, assessment of safety of veterinary medicines residues — namely data which should be included in the general evaluation of medicines.

At the end of 1988, the Commission proposed to regulate within the EEC international procedure for the etablishment of maximum residue limits (MRL) for all residues of veterinary drugs. The member states will not be able to prohibit imports of food from other countries if the community MRL is respected and will be obliged to stop entering the food which exceeds the MRL. The regulation adoption procedure will be completed by 1997.

In the successive paper, *Professor T. Juszkiewicz* (Veterinary Research Institute, Puławy, Poland) presented Polish laws and regulations designed for protecting human health from noxious effects of chemical and biological residues in food.

In Poland, the Ministry of Health and Social Welfare is responsible for all issues pertaining to public health. It cooperates with the Ministry of Agriculture in regard to food of animal and plant origin. Both pesticides and veterinary medicines are authorised for use and trade. The Ministry of Agriculture, following opinions of special committees (drug, food, registration of pesticides) sets out official lists of pesticides and veterinary medicines. The Veterinary Research Institute in Pulawy is responsible for the national system of control in regard to food of animal origin (residues of pesticides, heavy metals and veterinary medicines).

Under the chairmanship of *Dr K. Lapis* (Semmelweis Medical University, Budapest, Hungary) Session III was held on environmental tobacco smoke: science and metascience.

Dr F.R. Rosendaal (Leiden University Hospital, the Netherlands) took the floor as the first speaker of this session. He gave the epidemiological review of suspected risk factors for pulmonary neoplasm, chronic obstructive pulmonary diseases (asthma, bronchitic, pulmonary emphysema) and ischaemic heart disease. Risk factors for pulmonary neoplasm can be divided into several subgroups: active and passive smoking, occupational exposure (paper industry, petrochemical industry, asbestos, asphalt, rubber, nickel, beryllium), genetics, low socio-economic level, diet and nutrition (especially no beta-carotene), ionizing radiation. Chronic obstructive pulmonary disease risks comprise: active and passive smoking, occupational exposure to various industrial substances and employment, for example, in gold, copper, iron ore, hardrock mining. In addition, air pollution, pesticides, food preservatives, food colouring agents, genetics and many other risk factors should be mentioned. All kinds of allergens are risk factors for asthma.

In the case of ischaemic heart disease, apart from classic ones such as smoking, high blood pressure and high level of cholesterol, other risk factors occur like clotting parameters, lipid fractions (LDL, HDL, VLDL, lecithin) diabetes and all kinds of personality traits (anxiety, depression, nervousness) as well as working more than 60 hours a week.

In summary, *Dr Rosendaal* stated that the number of suspected risk factors for lung cancer and cardiorespiratory diseases is overwhelming in sheer size and heterogeneity. The evaluation of these factors needs a very critical approach.

Epidemiology at low level exposure was presented by *Dr C. Vutuc* (University of Vienna, Austria). Epidemiology is a comparative science. By analysing the differences in the distribution, one is able to draw conclusions about the cause of diseases under study and about preventive measures even if mechanisms which evoke diseases are unknown. When the risk of disease is high, epidemiology is an excellent analytical instrument. The best example is the discovery of tobacco related diseases, in particular lung cancer. On the other hand, when the risk is small, differences in the studied population are also small, and interpretation of the results becomes very difficult. This is the situation in the discussion about relationship between low exposure to smoke (passive smoking) and lung cancer.

The analytical instruments used in epidemiology are prospective and retrospective studies. In both studies bias and confounding can occur when a study is not properly planned, performed and analysed or when the results are not properly interpreted. They may also occur when effect of uncontrolled variables on the studied factor is not taken into consideration, what can produce an incorrect assessment of the risk. In order to link the effect with the cause, some criteria of judgement have to be met: consistency, the magnitute of the risk, dose response, specificity, coherence, biological plausibility, experimental support.

Professor H. Magnussen (Krakenhaus Grosshansdorf, FRG) presented own clinical investigations done in his hospital in order to answer one single question whether symptoms of bronchial asthma do increase when a patient is exposed to tabacco smoke (passive smoking). An exposure chamber with a smoking machine was constructed. The particle density in the chamber was more than 2 000 $\mu m/m^2$ and the carbon monoxide concentration was about 20 ppm. A group of 18 adult patients and 11 children was investigated. The patients suffered from bronchial asthma, characterised by "bronchial hyperresponsiveness", namely overreactivity of respitory airways to stimuli. Any change in lung function parameters was measured by spirometry or by whole body plethysmography. Histamine or metacholine produces in patients with bronchial asthma the so called air flow obstruction. The studies of lung function in adult asthmatics exposed to tabacco smoke did not show any changes neither before nor after exposure in comparison with the control group. Patients exposed to smoke complained about irritation of eye, nose or throat but none of the patients suffered or claimed of cough or chest tightness. Similar subjective symptoms were observed in children exposed. Neither cough nor chest tightness was observed in these population.

In summary, it should be stated that acute smoke exposure, with 20 ppm carbon monoxide for one hour, does not change either lung function or bronchial responsiveness in adults or children with bronchial asthma.

The issue of cardiovascular diseases evoked by exposure to smoke was discussed by *Dr J. Thiery* (University of Munich, FRG). The coronary heart disease is one of the major killers in the world. A great number of risk factors for this disease is well known, but the level of cholesterol, atherogenic lipoproteins and acute smoking play the central role. There are no experimental studies that can demonstrate a definite effect of passive smoking on the development of atherosclerosis. Critical points apply to epidemiological studies, so far performed and published because of difficulties encountered in establishing the magnitute of exposure which should comprise smoking habits of persons living in the same household. These studies did not indicate the relationship between passive smoking and coronary heart disease.

Relationships between exposure to tobacco smoke and lung cancer were presented by *Professor D. Schmähl* (German Cancer Research Center, Heidelberg, FRG). In his opinion there is no doubt that 85–90% of all lung cancers occur in active smokers. In the case of squamous cell carcinoma there is a very fine dose response relationship between the number of the cigarettes smoked

daily and the relative risk of getting this disease. Filter smoking reduces the risk by 20—30%. That means that the dosage of tobacco smoke is very important for the relative risk. It should be remembered when active and passive smoking is compared. An addition, one should be aware of 30—40 year latency of lung cancer, hence present cases result form smoking in 1950's.

Coming to the toxicological point of view, tobacco smoke compounds which may be responsible for the induction of lung cancer, are very important. There are a lot of them, polycyclics, nitroso compounds, polonium, nickel and cadmium compounds just to mention a few. Ciliotoxic compunds which are able to destroy the functions of the celia in the bronchial epithelium, important for the self-cleaning of the bronchioles, also play an essential part. Tobacco smoke compounds are the same in active and passive smoking, however, the concentration of inhailed carcinogens is much less in passive smoking. In passive smokers practically no increase of mutagenicity was indicated by means of the Ames test, whilst in active smokers there is a dramatic increase of mutagenicity.

In this presentation like in previous ones it was stressed that the risk of passive smoking in comparison with active smoking is really small.

Each session was concluded by the panel discussion. To sum up, debates of the Toxicology Forum drew nearer issues of legal and methodological regulations existing in the area of toxicology both in Eastern and Western Europe. A general conclusion is that these regulations have to be harmonized for all European countries, in order to facilitate partnership contacts in such areas as import, export, supply and use of chemical compounds. Such harmonization will prove to be of great value in view of future integration of Europe.