Proceedings of the Workshop on Risk Assessment and Risk Management of Toxic Chemicals

Place : National Institute for Environmental Studies
16-2 Onogawa, Tsukuba, Japan

Period : 19 February (Wed) to 21 February (Fri), 1992

Edited by Takashi MIURA, Yuko SOMA and Chiharu TOHYAMA

National Institute for Environmental Studies

Organizing Committee

Dr. Michinori Kabuto
Head
Urban Environment & Health Research Team
Regional Environment Division

Dr. Akira Koizumi ***(Chairman)***
Director General

Dr. Takashi Miura ***(Executive Organizer)***
Principal Researcher
Regional Environment Division

Dr. Masatoshi Morita
Director
Environmental Chemistry Division

Dr. Masaru Sagai
Head
Air Pollutants Health Effects Research Team
Regional Environment Division

Dr. Yuko Soma ***(Treasurer)***
Head
Chemical Exposure and Health Effects Research Team
Regional Environment Division

Dr. Kazuo T. Suzuki
Professor
(Former Chief of Environ. Health Sciences Division)
Faculty of Pharmaceutical Sciences
Chiba University

Dr. Tsuguyoshi Suzuki
Professor (Univ. of Tokyo) and Acting Director
Environmental Health Sciences Division

Dr. Chiharu Tohyama ***(Secretary)***
Chief
Experimental Pathology and Toxicology Section
Environmental Health Sciences Division

P R E F A C E

Akira Koizumi, M.D.

Director General, NIES

This workshop is a follow-up to the First NIES/US-EPA Workshop on Risk Assessment and Risk Management which was held here in the National Institute for Environmental Studies (NIES) in September 1989. It is worthy of special mention that immediately following that workshop, a comprehensive discussion on risk assessment and risk management was also held on the occasion of the IXth UOEH International Symposium and the First Pan-Pacific Cooperative Symposium both convened by President Kenzaburo Tsuchiya of the University of Occupational and Environmental Health, Japan (UOEH) in Kitakyushu City.

Recent advances in risk assessment and risk management research have made it worthwhile to convene this forum to share contemporary results and ideas as well as to discuss these urgent problems from both the scientific and policy making perspectives. A wide range of topics will be covered including risk identification, exposure assessment, risk assessment, risk characterization and risk management.

I thank all of you for participating in this important workshop.

Workshop on
Risk Assessment and Risk Management of Toxic Chemicals

19 February (Wed)

Afternoon: Registration; a short tour to the NIES (15:30-17:00).
Evening: Mixer (17:30-19:30) at Director General's Reception Room at NIES

20 February (Thr)

9:30 **Welcome Remarks:** Akira Koizumi (National Institute for Environmental Studies)

Opening Speech: Chairperson: Akira Koizumi

9:40 Common aspects of risk assessment and management in environmental and occupational health with special reference to small-scale enterprises Kenzaburo Tsuchiya (Univ. of Occup. Environ. Health)

Keynote Address: Chairperson: Keiichiro Fuwa

10:00 Recent research activities on risk analysis for chemical substances. Eiji Yokoyama (Institute of Public Health)

SESSION A (Risk Identification) Chairperson: Takesumi Yoshimura (Univ. Occup. Environ. Health)

10:30 Indoor air quality issues in buildings John Spengler (Harvard University, USA)

11:10 Health risk of environmental pollutants in China Yufeng Li and Shouren Cao (Institute of Environmental Health and Engineering, China)

--- Discussion ---

11:50 --- Lunch ---

SESSION B-1 (Exposure Assessment) Chairperson: Masataka Murakami (University of Tsukuba)

13:00 The total exposure assessment methodology (TEAM) studies: personal exposure to volatile organic chemicals, particles, and pesticides in air, drinking water and house dust Lance A. Wallace (US EPA)

13:40 Human exposure to airborne carcinogens/mutagens: preliminary survey on personal exposure and indoor/outdoor pollution by using highly sensitive analytical methods for PAHs and nitro-PHAs Kiyoshi Tanabe and Hidetsuru Matsusita (Institute of Public Health)

--- Discussion ---

SESSION B-2 (Exposure Assessment) Chairperson: Michinori Kabuto (NIES)

14:00 Routes of exposure to potable water contaminants. Julian B. Andelman (Univ. of Pittsburgh, USA)

14:30 Organotin compounds in coastal biota, Japan. Hiroaki Shiraishi and Yuko Soma (National Institute for Environmental Studies)

--- Discussion ---

SESSION C-1 (Risk Assessment and Risk Characterization) Chairperson: Masatoshi Morita (NIES)

15:10 Health risk assessment of monochlorodibenzofuran. Chiharu Tohyama, Seishiro Hirano and Kazuo T. Suzuki (National Institute for Environmental Studies)

15:30 Health risk assessment of dioxin and related compounds: consideration of the mechanism of toxicity. Thomas A. Gasiewicz (University of Rochester, USA)

--- Discussion ---

----- Break -----

SESSION C-2 (Risk Assessment and Risk Characterization) Chairperson: Yuzo Hayashi (National Institute of Hygienic Sciences)

16:30 Estimation of toxic dose of atmospheric compounds in Japan. Takashi Miura, Kiyoshi Tanabe and Yuko Soma (National Institute for Environmental Studies)

16:50 Toxicokinetics of trichloroethylene in the workplace. Akio Sato (Yamanashi Medical University)

17:20 Toxicokinetics of dioxin and related compounds. Jeremy J. Mills and Melvin Andersen (Chemical Institute of Industrial Toxicology, USA)

--- Discussion ---

19:00 --- Reception --- (Tsukuba Dai-ichi Hotel)

21 February (Fri)

SESSION C-3 (Risk Assessment and Risk Characterization) Chairperson: Tsuguyoshi Suzuki (NIES)

9:20 Health risk assessment of toxic metals. Monica Nordberg (Karolinska Institute, Sweden)

10:00 Environmental epidemiology of Minamata disease with special emphasis on its relevance to risk assessment of methylmercury. Hiroo Kato (National Institute for Minamata Disease)

--- Discussion ---

SESSION C-4 (Risk Assessment and Risk Characterization) Chairperson: Kazuo T. Suzuki (Chiba Univ.)

10:40 *In vitro* toxicity testing and risk assessment. John M. Frazier (Johns Hopkins University, USA)

11:20 Limb bud cell culture for *in vitro* teratogen prescreening. Junzo Yonemoto (National Institute for Environmental Studies)

11:40 Basal cytotoxicity data (BC-data) in human risk assessment. Björn Ekwall (Univ. of Uppsala, Sweden)

--- Discussion ---

12:30 --- Lunch ---

SESSION D-1 (Risk Management) Chairperson: Masaru Sagai (NIES)

13:30 Integrated simulation model for health risk assessment. Robert Kellam (US EPA, USA)

14:10 Health risk assessment/management of pesticides: principles and methodologies. Jun Sekizawa (National Institute of Hygienic Sciences)

--- Discussion ---

SESSION D-2 (Risk Management) Chairperson: Masaaki Naito (NIES)

15:00 Risk assessment of drinking water contaminated by herbicides and pesticides from golf links. Tohru Morioka and Akihiro Tokai (Osaka Univ., Japan)

15:30 Comparative risk analysis for priority setting. Si-Duk Lee and Lester Grant (US EPA, USA)

--- Discussion ---

16:30 **Closing Remarks:** Takashi Miura (National Institute for Environmental Studies)

List of Principal Participants

Dr. Julian B. Andelman
Professor
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, PA 15261
USA
Fax:1-412-624-3040

Dr. Melvin E. Andersen
Senior Staff Scientist
Chemical Indusry Institute of Toxicology
PO Box 12137
6 Davis Dr.,
RTP, NC 27709
USA
Fax:1-919-541-9015

Dr. Björn Ekwall
Associate Professor
Dept. of Toxicology
Univ. of Uppsala
Box 594,
S-751 24, Uppsala
Sweden
Fax:46-18-174253

Dr. John M. Frazier
Associate Professor
Dept. Environ. Health Sciences
Johns Hopkins University
615 N. Wolfe St.
Baltimore, MD 21205
USA
Fax:1-301-955-0116

Dr. Keiichiro Fuwa
Former Director General of NIES
1-20-2-506 Naka-machi,
Musashino-shi,
Tokyo 180
Japan
Fax: + 422-51-8199

Dr. Thomas A. Gasiewicz
Associate Professor
Dept. of RB & B/Toxicology
Univ. of Rochester
Rochester, NY14642
USA
Fax:1-716-275-6007

Dr. Yuzo Hayashi
Director
Biological Safety Research Center
National Institute of Hygienic Sciences
Kami-yoga, Setagaya-ku,
Tokyo 158
Japan
Fax: + 3-3707-6950

Dr. Michinori Kabuto
Head
Urban Environment & Health Research Team
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: + 298-51-4732

Dr. Hiroo Kato
Director General
National Institute for Minamata Disease
Minamata, Kumamoto 867
Japan
Fax: + 9666-3-3111

Mr. Robert G. Kellam
Chief
Pollutant Assessment Branch
OAQPS, US EPA
RTP, NC 27711
USA
Fax:1-919-541-5661

Dr. Akira Koizumi
Director General
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: + 298-51-2854

Dr. Si-Duk Lee
Associate Director
Environmental Criteria and Assessment Office, US EPA,
RTP, NC 27711
USA
Fax:1-919-541-0245

Dr. Yufeng Li
Science & Technology Agency Fellow
Air Pollutants Health Effects Research Team
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

On leave from the Institute of Environmental Health and Engineering (Assistant Fellow)
Chinese Academy of Preventive Medicine
Beijing, China
Fax:861-301-1875

Dr. Takashi Miura
Principal Researcher
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

Dr. Tohru Morioka
Associate Professor
Dept. Environmental Engineering
Osaka University
Osaka
Japan
Tel: +6-877-5111, ext. 5177

Dr. Masatoshi Morita
Director
Environmental Chemistry Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-2854

Dr. Masataka Murakami
Professor
Institute of Community Medicine
University of Tsukuba
Tennoudai, Tsukuba 305
Japan
Tel: +298-53-3045

Dr. Masaaki Naito
Director
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-2854

Dr. Monica Nordberg
Professor and Chairman
Dept. Environmental Medicine
Karolinska Institute
Box 60400
S-104 01 Stockholm
Sweden
Fax:46-8-314124

Dr. Masaru Sagai
Head
Air Pollutants Health Effects Research Team
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

Dr. Akio Sato
Professor
Dept. Environmental Health
Medical University of Yamanashi
Tamaho, Yamanashi 409-38
Japan
Tel: +552-73-1111

Dr. Jun Sekizawa
Chief
Division of Information on Chemical Safety
National Institute of Hygienic Sciences
Kami-yoga, Setagaya-ku,
Tokyo 158
Japan
Fax: +3-3707-6950

Dr. Hiroaki Shiraishi
Senior Scientist
Chemical Exposure and Health Effects Research Team
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

Dr. Yuko Soma
Head
Chemical Exposure and Health Effects Research Team
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

Dr. John Spengler
Professor
School of Public Health
Harvard University
665 Hunchington Av.
Boston, MA 02115
USA
Fax:1-617-432-3349

Dr. Kazuo T. Suzuki
Professor
Faculty of Pharmaceutical Sciences
Chiba University
Yayoi, Chiba 260
Japan
Fax: +

Dr. Tsuguyoshi Suzuki
Professor and Acting Director
Environmental Health Sciences Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

Dr. Kiyoshi Tanabe
Senior Scientist
Institute of Public Health
4-6-1 Sirokanedai, Tokyo 108
Japan
Fax: +3-3446-4314

Dr. Kenzaburo Tsuchiya
President
University of Occup. Environ. Health
Iseigaoka, Yahatanishi-ku,
Kitakyushu 807
Japan
Fax: +93-691-1865

Dr. Chiharu Tohyama
Chief
Experimental Pathology and Toxicology Section
Environmental Health Sciences Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-0471

Dr. Lance A. Wallace

Environmental Photographic Interpretation Center
US EPA
Building 166, Bicher Rd.,
Vint Hill Farm Station,
Warrenton, Virginia 22186
USA
Fax:1-703-557-0243

Dr. Eiji Yokoyama
Director General
Institute of Public Health
4-6-1 Sirokanedai, Tokyo 108
Japan
Fax: +3-3446-4314

Dr. Junzo Yonemoto
Senior Scientist
Chemical Exposure and Health Effects Research Team
Regional Environment Division
National Institute for Environmental Studies
16-2 Onogawa, Tsukuba 305
Japan
Fax: +298-51-4732

Dr. Takesumi Yoshimura
Professor

University of Occup. Environ. Health
Iseigaoka, Yahatanishi-ku,
Kitakyushu 807
Japan
Fax: +93-691-1865

Contents

Keynote Speech
and
Keynote Address

Common Aspects of Risk Assessment and Management in Environmental and Occupational Health with Special Reference to Small-Scale Enterprises

Kenzaburo Tsuchiya, M.D.
President, University of Occupational and Environmental Health, Japan
Kitakyushu, Japan

1. From occupational disease to environmental pollution

In my opening speech at this workshop I would like to discuss the relationship between occupational and environmental health, taking some examples from my experience in this field. I will show a picture of a patient with typical lead poisoning with wrist drop caused by paralysis of the N. radialis or the extensor muscle of the upper extremeties . This patient was introduced to me by a internist at the Keio University School of Medicine when I was working in the Department of Preventive Medicne of the same school. The patient had been referred by a community physician who suspected diabetic and alcoholic peripheral neuropathy, but one look at the patient was sufficient for the diagnosis of lead poisoning (Nakazawa et al, 1969). After I made this diagnosis I visited and inspected the pigment factory where the patient was employed. The workplace was heavily contaminated with yellow lead and some workers were wearing respirators. The factory yard was also covered with yellow lead dust. More important is the fact that the rooftops in the vicinity of the factory were also yellowish. This is a very good example indicating the relationship between the occupational environment and the community environment around a factory. Figure 1 shows relationship between a large industry and a smaller industry. This figure shows the analogy of an industrial structure to an ecosystem in terms of food chain. A large industry or establishment is the final consumer, like humans. As shown in the figure microorganisms such as bacteria, insects, plankton, etc. in the hydrosphere or landsoil are contaminated with man-made chemicals and eaten by larger organisms and often find their way into the human stomach. When you look at the health status of working populations, the healthier are found in larger industries, while the situation is not so good in smaller industries (Figure 2). The majority of the working population in Japan works in smaller establishments of 500 employees or less. Approximately 95% of the working population works in smaller establishments of 50 employees. Smaller enterprises tend to pollute their environment more than larger industries, as shown in a previous figure.

Figure 3 shows a diagram of my concept of the industrial ecological sciences, about which I have discussed in more detail at an earlier international meeting more in detail (Tsuchiya, 1991). From an international viewpoint industries in developing countries resemble smaller enterprises in developed countries.

2. Environment and health

Figure 4 shows the relationship between environment and health. As shown in the figure, some working environment (indoor) and community environment including individual human activity represented by the production and use of automobiles is linked to the district environment and finally to the global environment through the national environment. This relationship can be applied also to health issues. As shown in this figure, occupational health is linked to community or public health and living standards, including life style, resulting in a level of district health and finally the health status of all mankind. As Rogers (1960) pointed out many years ago, man's health status with genetic characteristics is the summation of the total effects of the environment. What I have here may be criticized as being over simplified or too conceptual. However, ethical issues are very important in coping with the environmental problems we face. Ethical issues are deeply related to culture (Douglas & Wildavsky, 1982). Without changing the culture of a district or a nation it is very difficult to assess and manage the risks. Nevertheless, even if one risk is properly assessed and managed, another risk may be generated by the introduction or intervention of a new technology. Thus, I believe that this kind of simple model should be repeatedly demonstrated and explained to everyone, particularly to lay people throughout the world via the educational system, media, etc.

3. Importance of small enterprises in relation to environmental health

As I mentioned repeatedly, improvements to protect health in the working environment and the general environment in or near small enterprises are urgently needed. However, realistically speaking, it is not necessarily responsibility of the government to give economic support to those industries, but rather to change their thinking regarding occupational health. With regard to occupational health in Japan, for instance, the principal approach has been centered on periodic health examinations rather than improvement of the work environment. It is also true that there have been very few papers concerning cost-benefit analysis in occupational

health. What I would like to emphasize here is that if more attention is paid to improvement of the work environment, more effective results will be seen in improvement of the general environment in the vicinity of those firms, with healthier conditions for the workers as well as for the community in general. Japanese people tend to believe that health examination by itself is sufficient preventive measure. This kind of thinking may be based on the traditional development of medicine in Japan. Although I do not have much time to explain this, one reason for this is the fact that the vaccination program was very effective and successful in preventing many communicable diseases since the introduction of Western medicine in the late 19th century. It could be also pointed out that the periodic health or medical examination was also very effective in the detection and control of tuberculosis. In other words, the priority of health maintenance has been placed on medical procedures, not on environmental engineering to improve health status. In the future, ergonomics will be more and more important in the information society of high technology. I would like to repeat that the improvement of working environment in small enterprises, especially in developing countries, will finally work to improve the global environment.

4. Conclusion

In this short presentation I have discussed the relationship of environmental pollution and health status among industries or establishments by size. Both environmental pollution and health status are closely related to the size of establishments, industrial sturucture or industrial ecosystem, comparable to the natural ecosystem. In discussing environmental pollution as related to health level, more attention should be paid to smaller-size enterprises. Small-size enterprises of less than 50 employees make up 95% of the total working population in Japan. I know that global issues including increase of CO2, acid rain, ozone hole, waste disposal, etc., are very important. But, there remain many crucial environmental issues in small-size enterprises even in developed countries. These are, of course, growing and increasing in developing countries. The source of global environmental pollutions originates in human activity, especially in small enterprises in technologically developed countries and due to rapid industrialization in developing countries. The large industries in the developed countries need to become more aware of their responsibility regarding the risk management of smaller enterprises and industrialization in developing countries in both technological and financial aspects.

References

Douglas, M. & Wildavsky, A. (1982): Risk and Culture, University of California Press, Berkeley

Nakazawa, T., Satowa, S. & Tsuchiya, K. (1969): Toukotsu shinkeimahi wo tomonatta namarichudoku no ichi-chikenrei to hatsubyo ni kansuru kosatsu (in Japanese) (A case report of lead poisoning with paralysis of N. radialis), Shindan to Chiryo 57(4):136-142

Rogers, E. S. (1960): Human Ecology and Health - An Introduction for Administrators, The Macmillan Company, New York

Tsuchiya, K. (1991): Comprehensive Assessment of Occupational and Environmental Health Problems: An Overview - A Proposal of Macro Approach: Industrial Ecological Sciences, Toxicology and Industrial Health 7(5/6): 53-58

Fig. 1

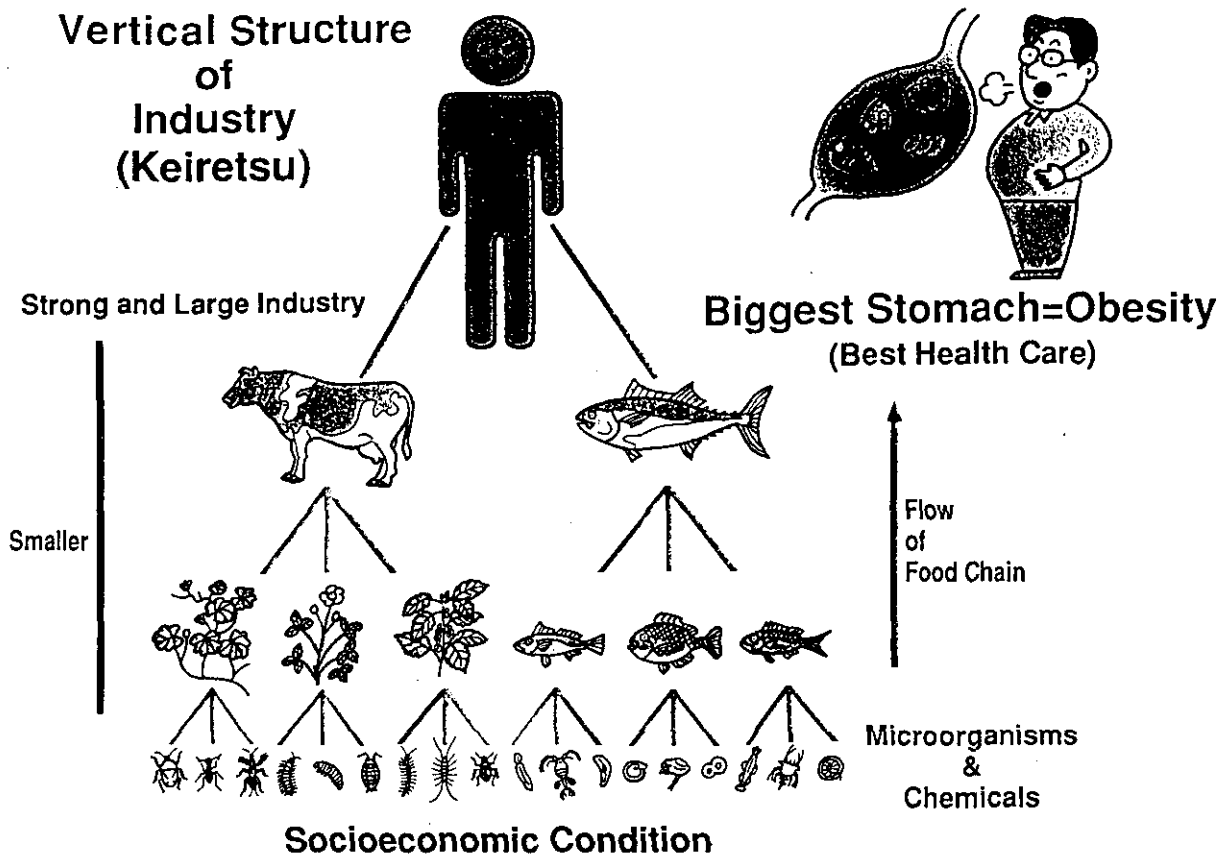

Vertical Structure of Industry (Keiretsu)
Strong and Large Industry
Smaller
Biggest Stomach=Obesity
(Best Health Care)
Flow of Food Chain
Microorganisms & Chemicals
Socioeconomic Condition

Fig. 2

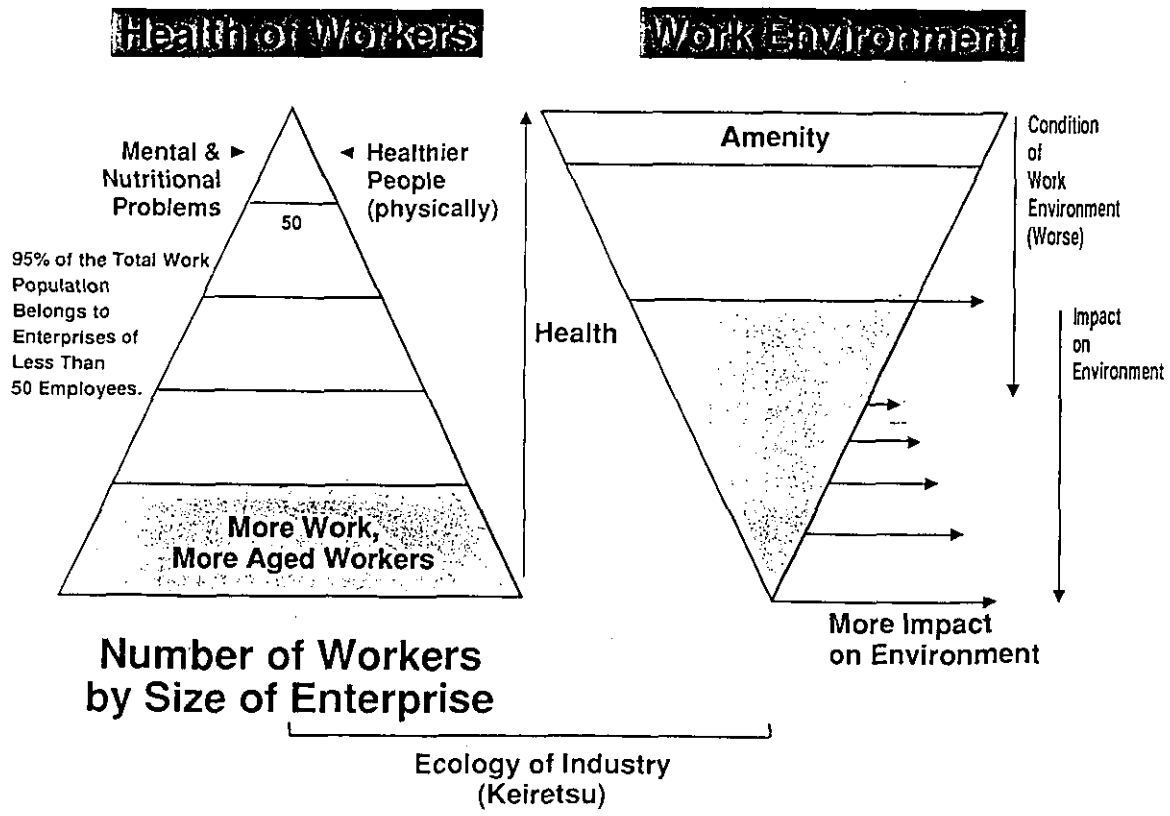
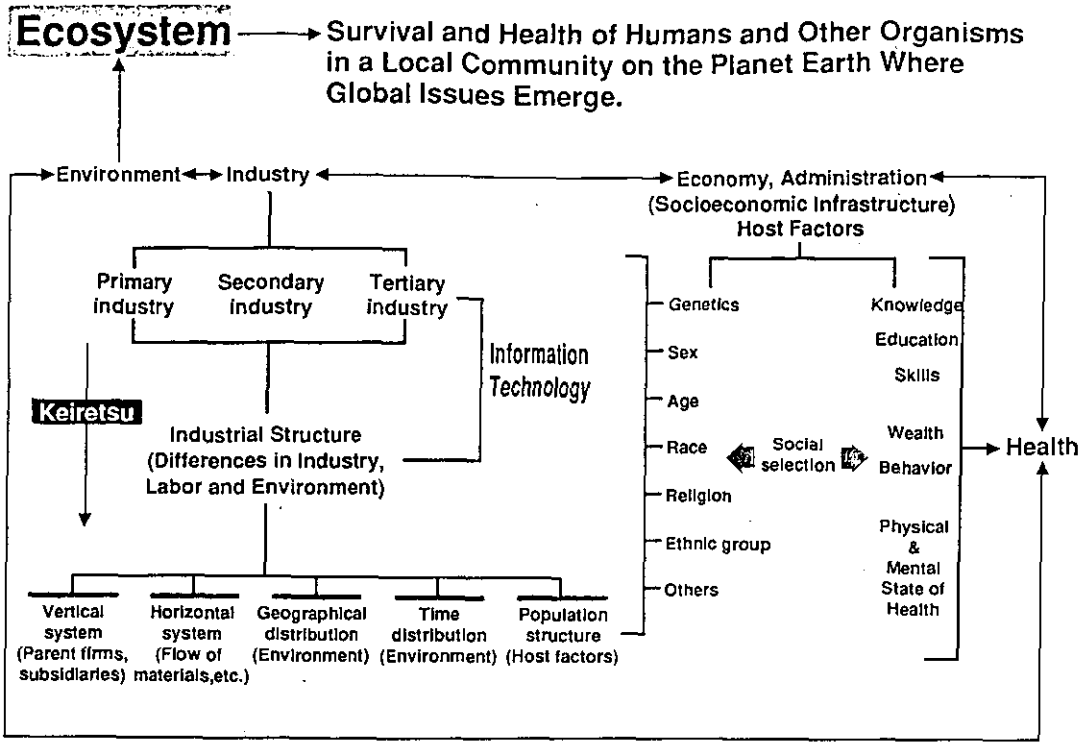

Health of Workers
Work Environment
Mental & Nutritional Problems
Healthier People (physically)
50
95% of the Total Work Population Belongs to Enterprises of Less Than 50 Employees.
More Work, More Aged Workers
Amenity
Health
Condition of Work Environment (Worse)
Impact on Environment
More Impact on Environment
Number of Workers by Size of Enterprise
Ecology of Industry (Keiretsu)

Fig. 3



Relationship Between Industrial Ecological System and Health Risk

Fig. 4

Environment and Health

1. $\int$ Working Environment → $\int$ Indoor Environment & Community Environment (Individual Human Activity) → $\int$ District Environment → $\int$ National Environment = Global Environment (Ecosystem of Living Organisms)
2. Occupational Health → Community (Public) Health or Living Standard Including Life Style → District Health → Health of All Mankind
3. $\int$ (Genetic Man, Total Effects of Environment) = Man's Health Status (Rogers, 1960)

Recent Research Activities on Risk Analysis for Chemical Substances

Eiji Yokoyama

The Institute of Public Health

An industrialization in Japan after the World War II was promoted by the marked improvement of science and technology, which resulted in a numerous number of various chemical substances got synthesized. Chemical substances which have been used for manufacturing various products in Japanese industries amount to over 48,000 and about 500 of the new are annually getting introduced in industries. With the rapid industrial expansion, Japan was certainly rebuilt economically, but it was also true particularly in the 1960s that its environments, in industries and communities, were more or less polluted with various chemical substances previously unexpected, occasionally resulting in serious health injuries.

Based on these experiences, Chemical Substance Control Law was enforced in 1974 in order to prevent environmental pollution with chemical substances like PCB, and provided for advance examination concerning the biodegradation, bioaccumulation and toxicity of new chemical substances. This law was amended in 1987 so as to bring about the repletion and betterment of advance examination corresponding to the appearance of situations which was not expected at the time of its enactment and various OECD guidelines for the international unification of safety assessment methods. Industrial Safety and Health Law was enforced in 1972 to prevent health damages of workers, and amended in 1977 so as to include advance examination of toxicities of chemical substances newly introduced in industries.

Basic Law for Environmental Pollution Control was enforced in 1967 to provide the basis of environmental pollution administration, and many environmental laws were subsequently enforced in order to practically regulate these environmental pollutions. These laws were almost similar in many aspects to those in the U.S. Thus, Japan has a fairly long history of preventing the health injuries and abating the environmental pollutions with chemical substances, but the quantitative risk assessment in a strict sense has not been used as the basis of regulating those chemical substances.

One of the first researches of risk assessment in Japan was conducted in the late 1970s - the early 1980s in the area of food-contamination with hazardous chemical substances. It was particularly remarkable in these studies that the importance of monitoring-system was emphasized as a tool of exposure assessment on chemical substances uptaken through the contaminated diet. A great impact on the subsequent development of the research of risk assessment in Japan was given by the US-Japan Workshop on risk assessment and risk management, the present author believes. Supported by Japan Society for Promotion of Science and the US National Science Foundation and the other organizaiton, the first workshop was held in 1984, and the second in 1987 with the objective to expand the bilateral dialogue on risk assessment and risk management. It was certain that the establishment of the Japan-Section, Society for Risk Analysis was promoted by the scientific stimulus from these workshops.

The Japan-Section, Society for Risk Analysis has now the individual member of about 250 with various disciplines, and annually publishes the journal and helds the scientific meeting. Like at other

meetings, individual reports in addition to the plenary speech and the symposium are presented at each meeting over 2 days recently.

The administrations which are in charge of regulating chemical substances and environmental pollution have been recently concerned about risk assessment and risk management, and have taken the initiatives in several kinds of its research. For instance, the studies of fundamental systems to evaluate harmful chemical substances and of feasibility of operating such a system were conducted during 1984-1987 with the Grant for Health Science. As an extension of these studies, a large project concerning comprehensive safety measures of chemical substances are now in progress; this project consists of studies on (1) the improvement of the risk assessment methodology, (2) the improvement of test systems on toxicity, and (3) the exploitation of risk management methodology.

With these circumstances, the research of risk assessment and risk management on chemical substances are advancing year after year in Japan, but not necessarily fully active yet. As Covello et al.(1988) pointed out, negotiation and consensus-building was rather regarded as important in the approach to decision-making on the regulation of environmental pollutions, while rigorous scientific analysis and open adverserial processes was regarded as important in the approach in the U.S. Something to support this approach may have influenced on the use and research of risk assessment and risk management in Japan at least in the past.

The increasing trend in mortality with malignant neoplasms is evident in Japan: its mortality ($/10^5$) was 77 in 1950, and steadily continued to increase reaching 177 in 1990. It is commonly recognized

that various chemical carcinogens in all media of our lives are greatly participated in malignant neoplasm incidence, and it is also widely recognized that a methodology to comprehensively evaluate carcinogenic effects of those chemical substances, that is, risk assessment is required to properly decide how to manage it. The present author hopes that this workshop will contribute to the further development of the research of risk assessment and risk management on chemcial substances in Japan.

Covello, V.T. et al. (1988) Cooperation versus confrontation: A comparison of approaches to environmental risk management in Japan and the United States. Risk Analysis 8:247-260.

Session A

Risk Identification

INDOOR AIR QUALITY ISSUES IN BUILDINGS

John D Spengler, PhD
Harvard University, School of Public Health

ABSTRACT

The modern building is a complex environment. Occupants can be exposed to a variety of chemical and biological contaminants. The physical environment can produce stress and irritation if the thermal, acoustical, and lighting conditions are not within acceptable ranges. The design, operation and maintenance of a building's ventilation system are critical factors associated with managing the internal climate.

However, ventilation systems are not the only cause of complaints and illnesses among building occupants. Fibres, organic chemicals, combustion exhaust, and microorganisms are some of the contaminants associated with building problems. Finding the causes for sick building syndrome will require new approaches. Development of biomarkers for irritation and new animal assay techniques are encouraging. The application of clinical approaches to field epidemiology might reveal why a subset of individuals appear more sensitive to low levels of contaminants.

The responsibilities for indoor air are shared by many within a society. The solutions to indoor air problems will require the involvement of many professional groups, government, and trade associations, as well as the research community.

1. INTRODUCTION

Throughout the developed and developing world, countries are experiencing urbanisation where the infrastructure will be built and rebuilt. By the year 2000, half the population of developing countries will live in urban areas. Fifty of the world's 66 largest cities, cities with a population exceeding 4 million, will be developing countries. Half of the residents of these new expanding cities will be living in unplanned settlements. Seventy percent of those dwellings will be headed by women. Without a doubt, housing is linked to health through water, sanitation, ventilation, air pollution, pests, and noise among other factors. Similarly, other structures such as offices, industries, and commercial and transportation facilities affect the health and safety of occupants.

The indoor environmental conditions of buildings are important because most of mankind will spend more that 80% of a lifetime inside some built structure. In addition, structures that harbor biological agents, outgas chemicals, have combustion sources, suck in soil gases (e.g. radon), contain fibrous materials, and are inadequately ventilated may be pathologic, placing occupants at risk. This presentation will highlight the issues related to the indoor environment of buildings.

2. BACKGROUND

Structures are designed to serve human function. They provide protection against the elements and are often secure and comfortable places to serve a myriad of human activities. To construct, operate and maintain buildings one must consider many factors such as labor and material costs, and architectural and functional form. Often, the issues of indoor environmental quality are not considered beyond compliance with codes (e.g.

many factors such as labor and material costs, and architectural and functional form. Often, the issues of indoor environmental quality are not considered beyond compliance with codes (e.g. lighting, electrical, safety, sanitation, ventilation).

Issues like indoor sources or entrainment of outdoor contaminants are not often considered until complaints or illnesses occur in the building. This is unfortunate because the components of indoor air quality are straight forward. There are four relevant factors: *sources, mixing volume, dilution (air exchange or ventilation) and removal. Sources* may be continuous, controlled or influenced by human activity or dynamically coupled to air exchange. *Mixing volume* refers to the actual volume of a room, floor or building into which contaminants are emitted, transferred, mixed and diluted. Often this is not the physical dimensions of the space because barriers, accomplished with mechanical fans that supply and/or remove air from the interior spaces. In the absence of fans, pressure gradients caused by temperature and wind are responsible for most of the air exchange in structures. This type of air exchange will be more variable then a mechanical system. But even a mechanical system may not be designed properly. Further, the operation and maintenance of heating, ventilation and air conditioning systems (HVAC) can vary substantially within a building over time and among buildings. As a result, occupants of mechanically ventilated buildings may not be receiving sufficient amounts of air to dilute contaminants from indoor sources. *Removal* is caused by physical/chemical processes that decrease the concentration indoors, not by air exchange. If the ventilation rate is higher than the removal rates for contaminants and the source is indoors, then the concentrations will be determined primarily by the air exchange rates. On the other hand, if physical/chemical removal rates for indoor contaminants are high then concentration will be determined primarily by the removal mechanisms. Mechanical air cleaning devices can amplify the physical and chemical removal processes and provide a means for improving indoor air quality. Little is really known about the chemical reaction rates of most indoor gaseous contaminants. Recent studies indicate the complexity of gas, particle and surface material interactions that are possible indoors.

3. SOURCES OF INDOOR CONTAMINANTS

Sources of indoor contaminants can be classified according to physical, chemical, and biological properties; they can be classified by physiological or toxicological effects; or they can be described as materials and furnishings that have the potential to produce contamination. The latter classification scheme is more familiar to a wider audience. Therefore, Table I lists some of materials that are commonly used in buildings. Depending on the specific materials actually present and the activities of the occupants, the contaminants listed in Table II might be measured in the indoor air. It should be noted that in the broader definition of indoor environmental quality other factors affecting comfort and health might be included - a partial list of these appears in Table III.

Table I. Materials in Buildings that Can Contribute to Contamination

Work Site/Foundations

Radon, Contaminated Soils/Water, Insecticide Treatment, Fertilizers, Waterproofing

Structure

Caulking, Sealants, Glazing Compounds, Preservatives, Curing Agents, Oil Paints, Lacquers, Biocides in Waterbase Paints

Insulation

Man-made mineral fibres in ducts and on surfaces
Asbestos fire retardant or decorative applications to surfaces
Asbestos thermal insulation of pipes, Urea formaldehyde foam insulation

Interiors

Surface Coverings: plywood, particle board, carpet and backing, ceiling tiles (resins, dyes, adhesives)
Furnishings: particle or chipboard, textiles
Cleaning Compounds
Equipment: copying machines, humidifiers, computers, unvented or faulty heaters, gas oil or gasoline-powered engines
People, Pets and Insects: bacteria, viruses, allergens, odours, tobacco smoke
Water Damaged Surfaces, Standing water, Condensation, Microorganisms
Biocides, Insecticides, Pesticides applications to surfaces or additives to steam/water systems

Table II. Indoor Contaminants and Example of Sources

CONTAMINANTS	EXTERNAL SOURCE
NO_2, CO, Benzene, BAP, PAH	Tobacco, kerosene combustion
Formaldehyde	Particle board, fabrics
SO_2	Sulfur in fuel oils
Endotoxins	Bacteria in water sprays, fountains, etc
Fungi nutrient	Growth on wet surface with organic
Legionella	Cooling tower water, shower heads
Chlordane, Diazinon, Heptachlor	Termiticides, pesticides
Antigenic Material	House mites, cockroaches, cats, dogs
Aromatic Organic Compounds (Benzene, Styrene, Xylenes)	Gasoline, consumer products, building materials
Chlorinated Organic Compounds (chloroform, tetrachloroethylene trichlorethane)	Cleaning agents and solvents, mothballs, deodorizers, fresheners

Table III. Physical factors to be Considered for Indoor Environmental Quality

PARAMETER	CONSIDERATIONS
Temperature	Range, temporal and spatial variation, vertical gradients
Humidity	Range and variation
Air Flow	Velocity at different heights, across skin surfaces
Static Electricity	Electric sparks, particle deposition
Lighting	Intensity, windows, glare, spectrum
Heating and Cooling	Radiant heat loads and gradients across body, latent heat (humidity issues), sensible heat (temperature and air velocity issues), localised positioning of heating or cooling sources or air distribution
Housekeeping	Dustiness, soiling, neatness, storage
Psychological	Control of environmental conditions at individual level (windows, thermostat, supplemental system), job-related factors
Vibration and Noise	Low frequency oscillations, properties of noise (loudness, frequency, etc.)

Long before the energy crisis there was a major change in how buildings were designed and constructed. Increasing urban land costs, as well as labor and material costs, led to innovation in construction. Now on-site steel or concrete structural frames are erected, then off-site prefabricated components are built to specification, brought on-site and hung on the frame. What results, for the most part, are sealed environments.

The indoor climate of sealed buildings is determined by HVAC systems designed to code requirements. Most buildings codes follow the recommendations of ASHRAE (American Society of Heating, Refrigerating, and Air Conditioning Engineers). The current ASHRAE standard 62-1989 recommends a minimum ventilation rate of 15 cubic feet per minute per person (cfm/person). Office building work areas should be ventilated at 20 cfm/person. A smoking lounge should have between 50 and 60 cfm/person. Previous ASHRAE ventilation standards suggested 5 to 10 cfm/person in the presence of smoking would be sufficient for a comfortable indoor environment for at least 80% of the occupants. The revised standards recognize that materials, furnishings, and equipment as well as occupants give rise to odorants and irritants that must be diluted and removed. However, it should be noted that ASHRAE ventilation guidelines are consensus standards and not based on scientific consideration of health and irritation effects for many contaminants found indoors. It is likely that ASHRAE ventilation guidelines will be altered in the future.

The ventilation problems facing facility managers are numerous. Many modern buildings are sealed without windows that can be operated by individuals. The HVAC system has to satisfy many locations throughout the building without localized adjustments. Many of these buildings have HVAC systems designed to meet the earlier versions of the ventilation code and are difficult to adjust to new code. Further, variable volume units were designed to meet thermal requirements not necessarily fresh air requirements. Adequate temperature can be maintained within an occupied space by increased recirculation, ventilation air or reducing the total air supply. This type of HVAC unit in modern sealed office buildings have been associated with numerous complaints. Even with other HVAC systems the economic incentives to reduce operational expenses often have HVAC systems on reduced fresh air intake and/or reduced operating hours.

4. EXPERIENCE WITH PROBLEM BUILDINGS TODAY

Estimates vary widely as to the percentage of buildings that have unacceptably high complaint rates or actual outbreaks of illnesses among the occupants. Some estimates suggest that among 4 million, medium to large, commercial properties in the U.S. 20% could be considered sick buildings and another 30% have the potential of becoming problematic. At these rates it is not difficult to conclude that indoor environments are costing billions of dollars annually in medical costs and lost productivity.

Despite the recognition of indoor air quality (IAQ) problems in buildings for almost two decades, there is insufficient understanding about the physiological and psychological basis for human response to many of the chemical contaminants and physical conditions that comprise the indoor experience in the "modern" building. Codifying building investigations provides some insight, but variation in criteria results in a disparity in estimate of contributing causes. There is general agreement that sick building complaints (Table IV) are distinct from illnesses, allergies, or organ dysfunction that are amenable to diagnostic evaluation.

Table IV. Common Symptoms

Eye Irritation	Shortness of Breath
Dry or Scratchy Throat	Cough or Hoarseness
Headache	Dizziness
Fatigue	Nausea
Sinus Congestion	Sneezing
Skin Irritation	Nose Irritation or Bleeding

Unlike diseases or immunological responses, sick building syndrome (SBS) complaints within a building may come from many sources or a combination of conditions. It is axiomatic to say buildings are complex. With a heterogeneous population, it is not surprising to have diverse complaints without definitive association with causative agents or comfort factors. We are just beginning to conduct the research critical to understanding irritation response.

In the United States, buildings have been investigated by NIOSH, research laboratories and many private organizations. The procedures and instruments

recommended for investigating buildings are described in many books, articles and government manuals. The principle findings are summarized in this article.

Since the mid-1970's, NIOSH has been requested to conduct Health Hazard Evaluations (HHE's) in offices (80%), schools (13%) and health care facilities (7%). Through 1988, 529 investigations had been conducted that provide a general pattern to problems that have occurred. Table V summarizes NIOSH's experiences.

Table V. NIOSH Indoor Air Quality Investigations (Seitz 1990)

Classification	Buildings	%
Inside Contamination	80	15
Outside Contamination	53	10
Building Components	21	4
Microbial Contamination	27	5
Inadequate Ventilation	280	53
Unknown	68	13
	529	100

Building materials associated with 4% of the investigations include UFFI, particle board, plywood, glues and adhesives, fibrous glass, organic solvents, and caulking compound among others.

Five percent of the investigations involved microbiological contamination. Bacteria, fungi, protozoa and microbial products (e.g. endotoxins) have been found in ventilation systems, humidifiers, ice machines and water-damaged carpets, furnishings and building materials.

Contaminations from sources external to the building have been associated with complaints inside buildings in 10% of NIOSH's investigations. Soil gases, garage fumes, discharge vents, road way construction, and power and industrial sources have all been linked to indoor contaminants.

Contaminations can be generated indoors from sources such as laser printers, copying machines, pesticides, boiler additives (e.g. diethyl ethanolamine), tobacco smoke, and cleaning agents. These types of sources have been listed to complaints in 15% of the investigations.

More than half (53%) of the investigations concluded that complaints were associated with inadequate or faulty ventilation. Deficiencies contribute to temperature, humidity problems, draftiness, stuffiness, and electrostatics, as well as other conditions. HVAC systems may not be maintained or operated properly. Pressure imbalances can occur and ventilation air may not be delivered and mixed thoroughly within the occupied space. Cross contamination of air from labs, shops, cafeterias, pools, and offices can occur.

NIOSH investigators acknowledge that their HHE's don't provide a clear etiology of SBS. Only the primary and most obvious causes are categorized. This leaves the impression that most problems could be alleviated with improved ventilation. This

may be a mistake if contaminant sources are not identified, reduced or eliminated. Symptoms might continue even after the ventilation system has been modified, but now a small portion of the population is affected. If sensitization to an agent is involved with a building illness, then simply improving ventilation without eliminating the source of contamination would delay reactions without curing the problem. NIOSH researcher, Wallingord, complains that half of the 53% "inadequate ventilation" cases didn't meet ASHRAE standard 62-1981 for outside ventilation and about a fourth did not meet ASHRAE standard 55-1981 for thermal and humidity conditions.

Woods and colleagues (1988) have conducted over 100 building investigations. Tables VI and VII reflect a recognition that multiple problems can occur within buildings. Their experience as well as other that of other independent investigators indicate that biological contamination is a substantially greater contributor to SBS (20-30%) than suggested by NIOSH interpretations.

Table VI. Types of Predominant Environmental Stressors (Woods 1988)

Types of Environmental Stressor	Frequency (%)
Chemical and particulate contaminants	75
with odour discomfort	70
Thermal discomfort	55
Microbiological contaminants	45
Nonthermal humidity problems (with eye irritation and mould growth from low- and high-relative humidities respectively)	30

Table VII. Frequencies of Occurrence of Physical Causes of Problem Buildings (Woods 1988)

Problem Category	Physical Cause	Frequency (%)
Design System	Inadequate outdoor air	75
	Inadequate air distribution to occupied spaces (supply, return devices)	75
Equipment	Inadequate filtration of supply air	65
	Inadequate drain lines, pans	60
	Contaminated duct work or duct linings	45
	Malfunctioning humidifiers	20
Operations	Inappropriate control strategies	90
	Inadequate maintenance	75
	Thermal, contaminant load changes	60

5. SICK BUILDING SYNDROME RESEARCH ISSUES

To date much of what has been learned about SBS has come from unsystematic case studies or investigations involving a few buildings. Often control or comparison buildings are inadequate to characterize differences in rates of symptoms that occur in case buildings. Even when investigations involving a larger population of structures yield observational data. The statistical associations do not resolve how and why certain people respond to very low levels of contaminants or subtle shifts in environmental conditions. Many investigations of SBS are undertaken even when the basic mechanism of response is not understood.

Nevertheless, some things have been learned about the SBS complex from the systematic study of buildings. Careful studies of town halls in Denmark have indicated that fabric covered surface areas and total VOC concentrations are related to complaints (Skov and Valbjorn, 1987). In the Swedish studies of schools by Norback (1991), risk factors for responding to a building's environment include personal and non-work place factors. If a person, as a child, had a mother who smoked or has a residential history of living in an urban area, they will have a higher relative risk for developing SBS. Building factors associated with higher complaint rates include electrostatics, wall-to-wall carpets, exposure to VOC's, dust and working with VDT.

British investigators assessed health and comfort conditions among several thousand office workers (Finnegan, Pickering and Burge 1984). Based on these observations, mechanically ventilated, air conditioned buildings without windows that open had among the highest rate of SBS complaints. These studies report rates higher among women, non-professional staff and public sector employees.

The fundamental approach to the study of SBS has been reconsidered. The current situation of assessing only a few buildings at a time, even when large populations within the buildings are included, is inherently flawed. Buildings should be considered as subjects in a cohort. Similar to epidemiologic methodologies, the power of a study to discern real differences and/or a statistically significant association with factors depends on sample size, outcome specificity and resolution of exposure. SBS occurs within settings that are potentially multifactorial. In studying a few buildings the power to detect effects is seriously compromised. Building studies will have to involve thousands of structures in order for analysis to control for possible confounders or covariates. Among the factors of interest will be function, geographic location, management structure, occupant demographic, season, health benefits, and the HVAC system among many others.

During the past 10 years, the emission rates for a variety of products have been determined. Contamination levels in many indoor environments have been profiled. Still, predicting who will complain of irritation and to which contaminants remains elusive. Several possibilities have been postulated and partially supported by animal and clinical studies.

Direct absorption of chemicals by conjunctive and nasal mucosa can cause inflammation and irritation. Altering neurologic function might explain how the trigeminal nerve is responding to irritant stimulation. Alteration of alveolar surfactants could change lung surface tension. This mechanism might explain decline

in some pulmonary functions as reported by Kjaergaard, Holhave and Pedersen (1991). Psychophysical interactions of odour detection and inducement of stress must be considered.

Unravelling the causative factors and mechanisms responsible for the diverse array of complaints associated with SBS will require clinical studies in combination with field investigations. From building investigations we should gleam information on the intensity, duration and frequency of exposures to specific contaminants and complex mixtures. Diagnostic techniques, developed in the laboratory, will have to be used in the field to characterize individual responses. Techniques such as nasal lavage, tear film break-up time, tear film inflammation markers, swelling of nasal mucosa, pain threshold sensation, alternation of breathing patterns, and skin conductivity are a few examples. Indoor air research in buildings will need these techniques to objectively confirm occupant responses.

In addition, the role of laboratory and clinical studies must expand. The application of ASTM's "Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals" (E981-84) has already been used to evaluate paint emissions (Hansen et al. 1991). Now, the cryogenic collection of VOCs in buildings can be generated in different concentrations under controlled laboratory conditions. Mice can be exposed to doses of complex mixtures directly. The dose-response curve for a depressed respiratory rate...the indicator of irritation...can be derived for mice. The relationship between animal irritation response and threshold limit values (TLV's) for individual chemicals has been established. Establishing a similar relationship for complex chemical mixtures found indoors will be an important step forward.

Individuals who report irritation responses in building environments need to be evaluated clinically. Such studies, already begun in Denmark, show distinct differences for several physiologic and psychologic variables between "normals" and those showing SBS complexes. These controlled exposure studies need to be conducted elsewhere. Chemical mixtures as they evolve from products or occur indoors should be used along with an expanded set of effects markers. Under these controlled conditions we hope to learn if additional mechanisms are involved in human responses.

A pathway suggested for multiple chemical sensitivity involves stimulation or direct chemical transmission by the olfactory nerve to the limbic areas. Measuring evoked potentials in the cerebral cortex and activity of the hypothalamus could be revealing.

6. PRESENT AND FUTURE CONCERNS

Against the backdrop of indoor air quality concerns, it is apparent that many sectors of the society are becoming involved. Just ten years ago, the topic of indoor air quality was still in the domain of relatively few researchers. Much of the early interest was stimulated by the potential adverse effects of energy conservation. Since that time, the topics of formaldehyde in insulation material, asbestos in schools and building and radon in homes have become widely recognized as indoor problems. Now many professional groups have active committees, specialty conferences and publications related to this topic. The commercial sector is exploring the market opportunities for new products, and building evaluation and remediation services. Governmental agencies have formed service groups conducted research projects and have considered indoor standards. In a few instances the courts are asked to resolve

personal injury suits by attributing culpability to the construction, operations and evaluation aspects of building performance. So, it is now clear that the interest in indoor environments has broadened beyond the research activities of a few academics who were charaterizing contaminants, measuring exposures and evaluating health effects. The interest in indoor environments is beginning to encompass a widening circle of disciplines and societal endeavours.

Despite the increased interest, much remains to be understood before healthful and safe indoor environments become the focus of preventative strategies. In theory, homes, offices and other structures would never become a health threat to their occupants. Moreover, structures can be designed, built and operated to promote health and provide comfort and security. Towards this goal Table VIII lists the responsibilities that a modern society should undertake.

Reflecting on the explosive rate of information relevant to indoor environments over the previous two decades, it is clear that we are in transition. In many cases the science has evolved from measurements and observations to predictive models and sophisticated component testing. The challenge of the 90's will be devising effective remediation and prevention strategies. However, significant obstacles remain. As the number of players expend, the quality of research and the efficacy of solutions becomes more diluted. Conflicting evidence on effects, product performance, evaluations, and abatement will make it more difficult for an unsophisticated marketplace to discern value. As those with commercial interests recognize profit in indoor air quality, governments and consumers will have to become vigilant. The role of governments to intervene on behalf of the public will be tested anew over labelling, material testing, codes, standards for performance, and licensing practitioners. Unfortunately, the need for government involvement comes at a time when public and private sentiment are resistant to further intrusion. This situation is exacerbated by the paucity of critical thinking about the policy aspects of indoor air. Formulation of policy will not be easy. Even when considering just private property the rights of individuals as owner, occupant, renter or non-adult family member are difficult to define when it comes to defining responsibilities for healthful indoor environments. While technical developments will eventually provide practical solutions, it is important that a process to formulate a coherent indoor public policy begin.

TABLE VIII. RESPONSIBILITIES FOR INDOOR ENVIRONMENTAL QUALITY

EDUCATION:

- Schools of architecture and engineering should expand curriculum to include indoor environmental quality design.
- Programs should be developed for facility managers that include indoor air quality (IAQ) problem recognition, prevention, and evaluation.
- Industrial hygiene and environmental health science curricula should address the special aspects of non-industrial indoor environments.
- Public and business administration education should include introduction to environmental health sciences that present environmental risk in the context of total human exposure. The important concepts of indoor environments will be an important component.
- Allied medical professions should be informed of the health considerations of indoor environments and the diagnostic approaches for evaluating problem homes, offices and other structures.

PROFESSIONAL SOCIETIES:

- Promote and maintain a high level of scientific integrity for publications, conferences and members.
- Develop guidance documents defining good professional practice for building diagnostics and operations.

TRADE ASSOCIATIONS:

- Encourage standardization of material and product testing.
- Promote truth in advertising, sales, and among members with respect to the safety and efficacy of products and/or procedures, including labelling.
- Provide technical guidance and training on construction, materials, control equipment and abatement techniques.

INDUSTRY:

- Expand the concept of product stewardship to include health, safety and efficacy of end product use. This includes simulated testing of products use to measure potential exposure, and evaluation of product effectiveness among others.
- Provide training to sales and service employees to properly install, operate, maintain equipment, furnishing, ducts, HVAC systems, etc., that effect IAQ.

COMMERCIAL FACILITIES:

- Provide healthful indoor environments through proper operation and maintenance of HVAC systems, selection of internal furnishings and equipment and overall design and maintenance.
- Recognise and respond to IAQ health and comfort concerns of employees in an open and comprehensive manner.

TABLE VIII. RESPONSIBILITIES FOR INDOOR ENVIRONMENTAL QUALITY (CONT.)

PROFESSIONAL SOCIETIES (CONT.): . Promote public awareness. . Provide career training through short courses and seminars. **GOVERNMENT:** . Provide research support to better understand health, safety, productivity and comfort issues related to indoor environments. . Maintain good IAQ in government owned, rented, and subsidised buildings. . Provide guidance to procurement specifications with respect to products or construction related to IAQ. . Provide referral services or direct capabilities with respect to IAQ diagnostic investigations. . Advance public understanding on the risks associated with indoor contaminants and the efficacy of remediation. . Sponsor basic and applied research related to the development and testing of methods/techniques to effectively conserve energy in transportation, residential, commercial and public sectors that do not compromise indoor air quality. . Encourage the development of comprehensive policy on indoor environments.	**INDIVIDUALS:** . Responsible for proper use of products (i.e. application, ventilation, etc.). . Evaluation of indoor hazards (i.e. radon, asbestos, formaldehyde, microbiological contaminants) for protection of co-inhabitants, or prior to purchase and/or sale.

Health Risk of Environmental Pollutants in China

Li Yufeng Cao Shouren

Institute of Environmental Health and Engineering,
Chinese Academy of Preventive Medicine
29 NanWei Road, Beijing 100050, China

Summary

Coal is the major energy resourse in china. As in a manner that untreated coal is burnt exhustedly, about 2.3 million tons of coal-smoke are released each year, therefore the pollutants resulted from coal- burning are becoming one of the risk factor to human health.

Our investigation results show that the high incidence of Lung Cancer is closely related with domestic coal-burning air pollution at Xuanwei County, Yunnan province, and the respiratory disease is also increading with the growth of coal consumption(at the rate of 5 Percent) in big cities of china recent years. In order to seareh the potential effects of air Pollutants on human health, we have payed a attention to the components and the characters of aerosal particle either in Xuanwei County or in the five big cities, that is Beijing, Shanghai, Shengyang, Wuhan and Taiyue, All air Samples were collected on the glass fiber filters using an Anderson 2000 Casade impactor (5 Stages) with a flow rate of 0.566m^3/ min and determinated by the means of chemical method and animal test parllelly.

The cumulative distribution curve for differunt size of particles shown in Fig. 1 is a striaight line, indicating that the particles in atmosphere of Beijing (other cityes are the Same) showed a logarithmic distribution which means the pollution sources are stable. Relying

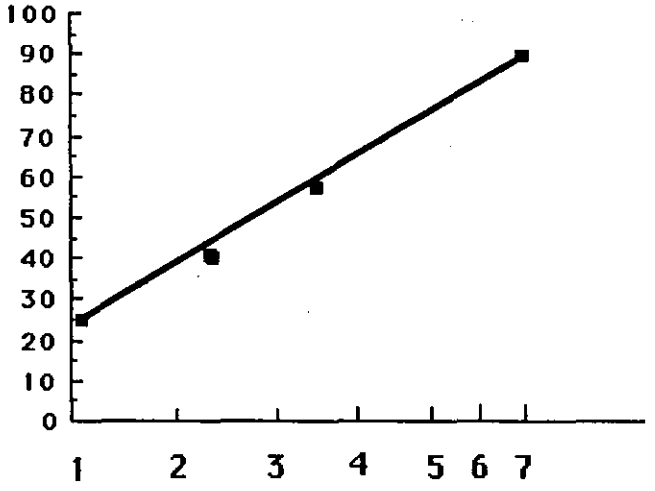


Fig 1, Size (μm)

Cumulative distribution of Particles

on the Mass Medium Diameter of inhable particle that is 1.8, 4.7, 4.6, 3.3, and 3.0 respectively in Xuewei. Beijing, Taiyue, Wuhan, Shengyang and Shanghai, We worked out that about 70 percent of particles were concentrated in the small size of particle which diameter is less than 3.0μm, and these kinds of particles may be easier absorbed by human

and caused a series of respirator disease. Especially, the concentration of particles is much higher in indoor air in Xuan wei County than in other Cities (Tablel), So we concluted

Table 1 Daily average Concentration of Particle(mg/m^3)

	Xuanwei	Beijing	Shang hai	Shenyang	Wuhan	Taiyue
in door	10.45	0.35	0.78	0.29	8.35	0.55
out door	0.24	0.68	0.23	0.65	0.44	0.46

indoor air Pollution plays a remarkble role to the high incidence of Lung Cancer in Xuan wei County, because there are a lot of harmful substance existed in the fine particles, in which one part of them are know to be potential carcinogens or harzadous, such as benzo(a) pyrene and the five or Six rings PAH. The result in Table 2 show that the concentrations of B(a) P and TOC on the air of Xuanwei are much higher than that of in Cities, and the Size distribution of B(a) P are close relation between indoor air and out door air in Xuan wei (r= 0.998). These results mean the coal- burming inside house is the single pollution source in Xuanwei County. (See Fig. 3) at the same time, the less the particle size is, the more the

Table 2 The distribution of total organic compond (TOC) and B(a) P in different size of Particle

Sample Site	conc. μg/100m^3	weight cumulative percentage (%)				
		<1.1	<2.0	<3.3	<7.0	<10
B(a)P BeiJing	2.40	42.2	67.4	78.10	87.96	100
Tai Yue	6.99	64.52	79.97	91.56	96.71	100
Xuan wei	7.58	74.09	90.91	97.77	98.88	100
TOC mg/m^3 (methane dichloride extrated)						
Tai yue	0.05	48.51	62.82	75.46	88.10	100
Xuan wei	27.8	69.97	84.48	89.94	94.04	100

concentration of B(a)P existed in , that had to be considered to be a factor of Lung cancer produced. In fact, the animal test and bioassays also supported the above conclusive.

In order to make sure of the relationship between the indoor air pollution from smoky coal burning and Lung Cancer, we have conducted studies of dose - response relationship between B(a)P concentration in indoor air and Lung cancer mortality in eleven communes of Xuanwei Since 1986. The observetion in Table 3 appears to show a close relationship between the percentage of households burning Coal and B(a) P Concentration and subsequent of Lung Cancer mortality in contrast to the percentage of households burning wood and smokless coal.

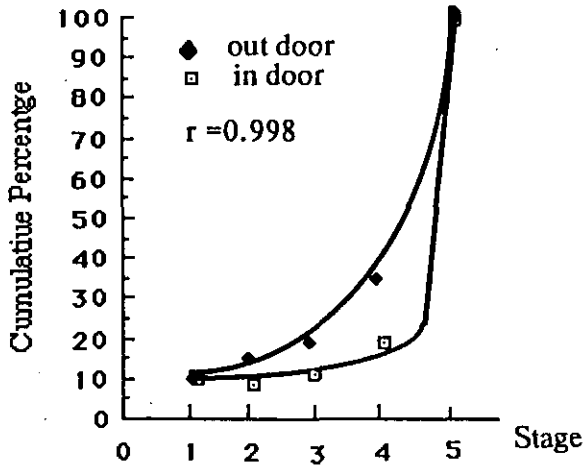


Fig 2

Table 3 Percentage of households burning fuel before 1958, and age- adjusted Lung Cancer mortality

Commun	Smoky Coal. %	wood %	Smokeless coal %	B(a)P μg/100m3	mortacity 1/100,000
Cheng guan	100.0	0.0	0.0	108.56	174.21
Lai bin	89.7	8.7	1.6	67.97	128.31
Rong bin	81.9	18.1	0.0	248.50	104.09
Longtan	78.0	22.0	0.0	55.98	22.96
Longchang	76.1	17.9	6.0	107.99	39.46
Bangiao	34.0	16.4	49.6	39.95	19.03
Bao Shan	87.1	12.9	0.0	46.37	9.18
Haidai	49.7	22.5	27.8	53.94	7.49
PuLi	35.2	52.0	12.8	28.62	7.49
Luo Shi	2.7	39.0	58.3	43.76	9.55
Re Shui	0.0	66.6	33.4	35.60	2.08

These data suggest that the more coal smoky and B(a)P concentration an individual breathes, the more likely he or she is to develop Lung Cancer.The result of statistical analysis shows a high correlation between B(a)P concentration in indoor air and Lung Cancer mortaity ($r=0.778$, $P<0.01$) This result also suggests that B(a)P concentration resulted from coal burning in indoor air plays an important role in developing Lung Cancer in Xuan wei , China.

Conclusion.

There are the same chemical and physical characters of particls in the atmosphere of china. the major air Pollutants are come from coal- burning. Especially, the B(a)P and PAH existed in the fine Parteles which size less than 3.0 μm, and gave a close correlation with the Lung Cancer mortality.

The situation of Lung Cancer developing is depended on the Concentration of carcinogen resulted from coal- burning.

Session B

Exposure Assessment

The Total Exposure Assessment Methodology (TEAM) Studies: Personal Exposure to Volatile Organic Chemicals, Particles, and Pesticides in Air, Drinking Water, and House Dust

Lance A. Wallace

United States Environmental Protection Agency
Building 166 Bicher Rd.
Vint Hill Farms Station
Warrenton VA 22091

For presentation at Workshop on Risk Assessment and Risk Management of Toxic Chemicals

National Institute for Environmental Studies
16-2 Onogawa, Tsukuba, Japan

INTRODUCTION

In 1979, the United States Environmental Protection Agency (EPA) began a series of studies known as the TEAM Studies (Wallace, 1987). Four TEAM studies have been carried out: on volatile organic compounds (VOCs), carbon monoxide (CO), pesticides, and inhalable particles. The experience gained from these studies has taught us several interesting--and sometimes surprising--lessons:

- o Sources are usually right under your nose
- o Exposures are often highest at home
- o Personal exposures usually exceed indoor levels
- o Indoor levels usually exceed outdoor levels
- o Industry and mobile sources together often contribute only 20-25% of total exposure

The basic concepts, methods, and findings of the major studies of human exposure are summarized, together with the research needs for the future in this emerging scientific discipline.

BASIC CONCEPTS

The major contribution of the TEAM Studies has been the emphasis on the following two concepts:

1) direct measurement of personal exposure using personal air monitors, with concurrent measurement of all other important routes of exposure, such as drinking water, food, and beverages. Often a measurement of body burden (e.g., exhaled breath) is made to identify routes of exposure that might otherwise be missed (e.g., smoking or dermal absorption).

2) stratified probability sampling to allow extrapolation of the results to a much larger population.

The first concept (direct measurement of exposure) has led to the development of a series of small, portable air quality monitors for measuring personal exposure. Such monitors have been developed or adapted by EPA for

- o VOCs: a battery-operated pump employing Tenax sorbent to collect 12-hour samples for analysis by gas chromatography-mass spectrometry (GC-MS).

About 25-30 VOCs have been targeted in various TEAM Studies of personal exposure and indoor air quality.

- o CO: a battery-operated pump with an electrochemical cell allowing continuous sampling over a 12-hour period. An attached data logger allows the participant to record his activities and integrate his exposure over each different activity or microenvironment.

- o pesticides: a battery-operated pump employing polyurethane foam (PUF) sorbent to collect 12-hour samples for GC-MS analysis. 32 pesticides were targeted in the Non-Occupational Pesticide Exposure Study (NOPES).

- o inhalable particles: a battery-operated pump with an impactor nozzle having a sharp cutoff at 10-micron aerodynamic diameter was employed to collect 12-hour samples of personal exposure to particles. A back-up filter treated with citric acid was employed to measure nicotine as an indicator of the contribution of tobacco smoke to exposure.

The second concept--statistical sampling of populations--has led to conclusions that are widely applicable to much larger populations than is normally the case. For example, the various TEAM Studies of VOCs between 1980-87 included about 800 participants, but these participants represented about 800,000 residents of urban, suburban, and rural areas in the East, Midwest, and West Coast. The CO studies of 1982-83 (Akland 1985; Wallace et al.,1988) included about 1200 participants, but represented more than a million nonsmoking residents of Denver, CO, and Washington, DC. The pesticides study findings (Immerman and Schaum, 1989) were applicable to the populations of Jacksonville, FL, and Springfield, MA. And the inhalable particle studies (Wallace et al., 1991) represented about 139,000 nonsmoking residents of Riverside, CA.

BASIC FINDINGS

The central finding of these studies is as follows:

The major sources of exposure to all chemical groups studied have been small and close to the person--often inside the home.

The basic data supporting this finding have been

published in the references cited above. The following discussion will focus on results obtained in the last few years for VOCs, CO, pesticides, and inhalable particles.

Recent TEAM Studies of VOCs

EPA's early studies of VOC exposures resulted in the important finding that all of the 10-20 prevalent VOCs studied had important sources in people's homes. Table 1 presents a summary of those data averaged over all personal air samples from all participants in the various VOC TEAM Studies up to 1987. Also included are estimates of carcinogenic risk and the proportion of exposure due to indoor sources.

The TEAM Study: CO (1982-84).

The goal of this study was to determine the frequency distribution of exposures to carbon monoxide (CO) for the nonsmoking adult population of Denver, CO and Washington, DC. The approach was to select more than 1200 persons representing about 2,000,000 nonsmoking residents and to measure individual exposures to CO for each subject over a 24-h (48-h in Denver) period. The major finding was that many more people (perhaps 100 times as many as expected in Washington) were exposed to levels of CO above the ambient air quality standard. The many outdoor monitors in each location (15 in Denver, 21 in Washington DC) were found to be unable to predict population exposures (correlation coefficient of <0.2, with an R^2 of 4%--virtually no explanatory power).

The TEAM Study of Pesticides.

The TEAM Study of pesticides (Non-Occupational Pesticide Exposure Study, or NOPES) was carried out in about 200 households in Jacksonville, FL over three seasons, and about 100 households in Springfield, MA over two seasons. A total of 32 pesticides were included as targets. The goal of the study was to determine the frequency distribution of exposures to pesticides in an expected high-use area (Jacksonville) and an expected low-use area (Springfield). All pesticides were collected on polyurethane foam, and analyzed by GC-MS or GC-ECD. Indoor, outdoor, and personal air samples were collected for all subjects. Dermal exposure was estimated for a subset of participants by providing a glove to wear during gardening; the glove was then analyzed for total deposition of pesticides. A small 8-home substudy utilized a specially designed sampler for household dust. Diets were recorded and food intake estimated using FDA Total Diet estimates.

Major findings (Table 2) included the following:

- Exposures from indoor sources were responsible for 90-99% of the total airborne exposure for most pesticides
- Banned pesticides (chlordane, heptachlor, aldrin, dieldrin) presented the greatest carcinogenic risk
- Tracking soil into the home appeared to be the major cause of exposure to many pesticides.

The TEAM Study of Particles

A large-scale TEAM Study of inhalable particles (Particle TEAM or PTEAM) completed the field work in November, 1990 in Riverside, California. Participants in both the pilot and full-scale studies carried a personal exposure monitor (PEM) to collect inhalable ($<10\mu$) particulates. A stationary indoor monitor (SIM) and a stationary ambient monitor (SAM) were located in the home and the backyard to determine indoor and outdoor concentrations. Outdoor air was also measured at a central site for the duration of each study. The filters were also analyzed for 15 elements. Nicotine badges were employed to determine the contribution of cigarette smoke to total particle exposure.

The personal and stationary monitors developed for this study proved to have excellent precision, dependability, and acceptance by the general public. They should form a useful additional tool to study personal and indoor exposures to particles and associated environmental pollutants; they have already been employed with good results in a study of lead exposures, and recently in a study of the increased exposures from the oil fires in Kuwait.

Outdoor PM_{10} and $PM_{2.5}$ concentrations throughout Riverside were generally well estimated from concurrent measurements at a central site. Indoor levels in homes were clearly dependent on outdoor concentrations, although they could be elevated by indoor activities.

Personal exposures were much larger than would be estimated from either indoor or outdoor concentrations (Table 3). This may be due to increased exposures in certain microenvironments or to a "personal cloud"--particles surrounding the person due to personal activities. Of 15 prevalent elements, 14 showed a similar 50% increase in the personal samples compared to the indoor samples. (The exception was sulfur, which showed no increase. The reason is not clear, although perhaps sulfur is associated

with very small particles that cannot easily be dislodged from carpeted or fabric-covered surfaces.) Further research on the microenvironments of interest and on the makeup of the personal cloud is desirable. These findings will also need to be considered in determining health effects and setting regulatory policy for particle exposures.

Summary of Findings

Each of these total exposure studies found that the major sources of exposure to most of the pollutants studied (including the 25 VOCs and 32 pesticides) were consumer products (air fresheners, stoves, pesticides) or personal activities (smoking, driving, dusting, bathing, drinking beverages) (Table 4). The major sources were seldom outdoor air or drinking water, and therefore could not be the "usual suspects": air or water discharges from industry, autos, municipal treatment plants, incinerators, landfills, etc.

OTHER RECENT STUDIES

Chamber study of half-lives of VOCs in the body.

The TEAM Studies have always included measurements of body burden, both to relate previous exposure to dose, and to check whether the measured routes of exposure in fact accounted for everything that entered the body. To relate breath measurements to exposure, we need to know how long the VOCs remain in the body. Therefore a chamber study was designed to make a direct measurement of the residence time of selected VOCs in the bodies of four volunteers (Gordon, 1988). The volunteers were first exposed in their own home to VOCs emitted from various common household sources (paints, solvents, cleansers, etc.). They then entered a clean-air chamber where they stayed for ten hours. During that time, about 15 breath samples were collected from each subject. Although the main goal was to determine the half-lives of the various chemicals, a second objective was to extend the breath monitoring method to evacuated canisters. Half-lives were very short (2-20 minutes) for all targeted VOCs in the blood; they appeared to cluster around 1-2 hours for the second compartment, with an indication that they might be 6-8 hours for the third compartment.

Total VOC Levels in TEAM Study Samples.

Few measurements of total VOCs in indoor environments or personal exposures are available. According to Molhave's study of persons exposed to synthetic mixtures of 22 common VOCs, the level at which frank effects was observed was 5 mg/m^3 (Molhave, 1985). Based on measurements of total VOCs in sick buildings, Molhave has estimated that the threshold

may be closer to 1-2 mg/m^3. Therefore it is of interest to examine the TEAM Study samples of personal and indoor air to determine what percentage exceed the possible threshold values of 1-5 mg/m^3, and to compare those findings with the corresponding percentage of outdoor air values. Following a feasibility study in 1986 to validate the proposed method for integrating under the curve of the mass spectrogram, 3000 TEAM Study samples were reanalyzed to determine the total organic loads collected by the Tenax cartridges. (This would be only a fraction of the total organics in the air sampled, since the Tenax does not collect polar organics and loses highly volatile nonpolar organics due to breakthrough.) The results (Wallace et al., 1992) indicated that the personal and indoor air samples exceeded 1 mg/m^3 about 60% of the time, whereas outdoor air samples exceeded that value less than 10% of the time. The distribution of personal air exposures was log normal, with a geometric mean of 1 mg/m^3 and a geometric S.D. of 3.5 (Fig. 1). About 250 (>10%) of the personal and indoor air samples exceeded 5 mg/m^3, the level at which Molhave found both subjective and objective neurological effects in his group of sensitive subjects.

Calculation of Long-term Exposures

To calculate lifetime risks, one must estimate lifetime exposures. However, most exposure measurements are short-term (days to weeks). How can one use such short-term measurements to calculate long-term (years to decades) exposure? Recently, a proposed method has been developed. This method allows long-term exposure estimates to be calculated from as few as two repeat measurements of the exposures of a selected population. The method was demonstrated using TEAM Study measurements in New Jersey and California. Certain chemicals (e.g. p-dichlorobenzene) appeared to have very large ranges in lifetime exposure, while others (e.g., chloroform) appeared to have small ranges of exposure.

MAJOR RESEARCH NEEDS IN HUMAN EXPOSURE

Measurement Methods Development

We have very little information about human exposure to certain very specific chemicals (e.g., asbestos) and to large classes of chemicals (e.g., very volatile organics such as vinyl chloride and methylene chloride, and polar organics such as a number of highly reactive chemicals that may be implicated in "sick building syndrome") that cannot now be measured adequately by existing personal monitors. On the other hand, if SBS and other conditions are caused

not by specific chemical exposure but rather by some synergistic combination of hundreds of low-level chemicals, then a monitor capable of measuring total organics may be required. Particles and acid aerosols also require some further development of personal monitors.

A major route of exposure for an important sensitive age group (toddlers) is household dust. Both pesticides and metals such as lead may be ingested with the dust at levels that might account for well over half of the child's total exposure. A need here is to validate a sampler recently developed by EPA that was designed to give reproducible results without "stripping off" the semivolatile organics from the particles.

Body burden methods are well developed on a research laboratory level for exhaled breath (VOCs, CO) but not for blood (VOCs). A need here is for the transfer of this technology to commercial laboratories and state agencies. A useful marker for NO_2 has not been found. In the longer term, biomarkers such as DNA adducts will be extremely useful in quantifying target organ dose.

Exposure-dose relationships need to be studied further, in order to make possible an estimate of one given a measurement of the other. For example, a single 2-minute measurement of breath levels could replace three or four measurements of air, drinking water, beverages, and food as a means of determining recent exposure. Because the chamber study indicated that many VOCs have extremely short half-lives of 2-20 minutes in the blood, a method for measuring single breaths repeatedly over a period of a few minutes is desirable; such a method has recently been developed and tested in the field (29).

Field Studies.

Assuming the household dust sampler mentioned above can be validated, a field study investigating pesticides and/or metals in dust would provide information now lacking on the exposure of toddlers.

A large-scale study of lead is desirable because of its serious effects and the many possible sources of exposure. Such a study could be combined with the study of dust mentioned above.

A study of "sick buildings" combining questionnaires on health symptoms, neurobehavioral tests, and measurements of nonpolar and polar organics could help define the causes, prevalence, and the extent of the impact on national productivity.

A large-scale study of chloroform (for those countries that chlorinate drinking water) would be desirable, since sources include volatilization from water use, dermal absorption during showering, bathing, and swimming, and ingestion of foods and beverages.

Models.

The basic need is for a model or set of models based on human activity patterns, since personal activities appear to be the prime sources of human exposure. Such models would have a stochastic component so that simulations could be run using distributions of physiological parameters, commuting times, etc. They would also need as input the results from the microenvironmental studies mentioned above. Only a few such models have been developed as yet (SHAPE for CO, SIMSYS for particles and NO_2), and they are in a nascent evolutionary stage. Early candidates for development of a model would be the volatile organics, particles, and NO_2, since a wealth of information has been developed on these substances.

Usually there are data gaps in the development of such models, however, and these must be filled by conducting special purpose microenvironmental studies in conjunction with model development. Improved activity pattern data bases are also needed, since no valid nationwide activity pattern data base exists in the detail required. Finally, the models must be validated by comparing their predictions with actual field data from human exposure studies such as TEAM. For those pollutants for which such studies have not yet been conducted, such as polar organics, emphasis must be given to solving the associated measurement method problems.

Summary.

The total human exposure research concept requires a balanced emphasis on

1) development of adequate measurement methods, both for personal exposure and body burden;

2) field studies, including both large-scale studies such as TEAM to establish frequency distributions of human exposure and smaller-scale focused studies to establish concentration ranges in important microenvironments; and

3) development of human exposure-activity pattern models, including validation of these models by comparing with the field study results.

REFERENCES

Akland, G. Hartwell, T.D., Johnson, T. R., Whitmore, R. (1985) "Measuring Human Exposure to Carbon Monoxide in Washington, DC and Denver, CO during the winter of 1982-83" Environ. Sci. Tech. 19:911-918.

Gordon, S.M., Wallace, Lance A. Pellizzari, E.D., and O'Neill, H.J. (1988), "Breath Measurements in a Clean-Air Chamber to Determine "Wash-out" Times for Volatile Organic Compounds at Normal Environmental Concentrations," Atmos Environ. 22:2165-2170.

Immerman, F.W. and Schaum, J. (1989) Nonoccupational Pesticide Exposure Study (NOPES). Final Summary Report, EPA Contract # 68-02-4544. USEPA, Research Triangle Park, NC.

Molhave, L., Bach., B., and Pedersen, O.F. (1986) "Human reactions to low concentrations of volatile organic compounds", Environ. Int., 12(1-4): 167-175.

Wallace, L.A. (1987) "Total exposure assessment methodology (TEAM) study: Summary and analysis", Vol. 1, Washington, DC: United States Environmental Protection Agency.

Wallace, L.A., Thomas, J., Mage, D. and Ott, W.R., (1988) "Comparison of Breath CO, CO Exposure, and Coburn Model Predictions in the U.S. EPA Washington-Denver CO Study." Atmos. Environ. 22: 2183-2193.

Wallace, Lance A., Pellizzari, E.d., Hartwell, T. D., Davis, V., Michael, L.C., and Whitmore, R.W., (1989) "The Influence of Personal Activities on Exposure to Volatile Organic Compounds," Environ. Res. 50:37-55.

Wallace, Lance A., Nelson, W.C., Ziegenfus, R., Pellizzari, E. (1991) "The Los Angeles TEAM Study: Personal Exposures, Indoor-Outdoor Air Concentrations, and Breath Concentrations of 25 Volatile Organic Compounds" J. Exposure Anal. & Environ. Epidemiol. 1:157-192.

Wallace, Lance A., Pellizzari, E.D., Spengler, J.D., Jenkins, P. et al. (1991), "The US EPA TEAM Study of Inhalable Particles (PM-10): Study Design, Response Rate, and Sampler Performance," paper #91-171.3 presented at the 84th Annual Meeting of the Air and Waste Management Association, Vancouver, BC. NTIS # PB91-182873.

Wallace, Lance A., Pellizzari, E., and Wendel, C. (1992) "Total Volatile Organic Concentrations in 2700 Personal, Indoor, and Outdoor Air Samples Collected in the U.S. EPA TEAM Studies," Indoor Air 1:(4).

Wallace, L. Duan, N. and Ziegenfus, R. "Can Long-Term Exposure Distributions be Predicted from Short-Term Measurements?" submitted for publication

Table 1. Average Measured Exposures to 12 VOCs for TEAM Study Participants; Associated Upper-Bound Lifetime Cancer Risks; and Contributions of Indoor Air to Total Risk

Chemical	Exposure[a] ($\mu g/m^3$)	Potency $(\mu g/m^3)^{-1}$ (X 10^{-6})	Risk (X10^{-6})	Indoor Air Contribution[b] (percent)
Benzene				
Air	15	8	120[c]	60
Smokers	90	8	720[c]	--
Vinylidene chloride	6.5[d]	50	320	86
Chloroform				
Air	3	23	70	80
Showers (Inhalation)	2	23	50	100
Water	30[e]	2.3[e]	70	--
Food & Beverages	30[e]	2.3[e]	70	--
p-Dichlorobenzene	22	4	90	98
1,2-Dibromoethane	0.05	510	25	40
Methylene chloride	6[f]	4	24	60
Carbon tetrachloride	1	15	15	20
Tetrachloroethylene	15	0.6	9	80
Trichloroethylene	7	1.3	9	80
Styrene				
Air	1	0.3[g]	0.3	70
Smokers	6	0.3	2	--
1,2-Dichloroethane	0.5	7	4	60
1,1,1-Trichlorethane	30	0.003	0.1	70

---

[a] Arithmetic means based on 24-hour average exposures of ≈ 750 persons in six urban areas measured in the TEAM Studies

[b] Based on backyard measurements in 175 homes in six urban areas

[c] The risk estimates for benzene are based on human epidemiology and are therefore mean as opposed to upper-bound estimates

[d] Six measurements exceeding 1000 $\mu g/m^3$ dropped from the calculation; inclusion of the measurements leads to an average exposure of 150 $\mu g/m^3$.

[e] These figures are in $\mu g/L$ or ppb rather than $\mu g/m^3$

[f] Based on only eight 24-hour indoor measurements in 1987.

[g] Source: US EPA (1983) Review and Evaluation of Evidence for Cancer Associated with Air Pollution, EPA 450/5-83-006.

Table 2. Upper-bound Lifetime Cancer Risks from Airborne Exposures to 23 Pesticides Measured in the NOPES TEAM Study

Pesticide	Exposure[a] (ng/m^3)	Potency (kg-d/mg)	Risk ($X10^{-6}$)	Indoor Air Contribution[b] (percent)
Banned Termiticides				
Heptachlor	71	4.5	90 (19)[c]	90
Chlordane	198	1.3	70 (15)	94
Aldrin	13	17	60 (13)	100
Dieldrin	3	16	14 (3)	92
Heptachlor Epoxide	0.4	9.1	1 (0.2)	80
DDE	2.2	0.34	0.2 (0.04)	100
DDT	0.7	0.34	0.1 (0.02)	88
Other Pesticides				
Dichlorvos	33	0.29	2.7	100
γ-BHC (Lindane)	6.6	1.3	2.5	100
α-BHC	0.5	6.3	1	100
Propoxur	100	0.0079	0.2	98
Hexachlorobenzene	0.3	1.67	0.1	90
Dicofol	2.6	0.34	0.05	100
o-Phenylphenol	58	0.0016	0.02	99
2,4-D	0.6	0.019	0.003	77
Atrazine	0.05	0.22	0.003	100
cis-Permethrin	0.4	0.022	0.003	100
trans-Permethrin	0.1	0.022	0.001	100
Chlorothalonil	0.7	0.011	0.002	28
Folpet	0.5	0.0035	0.0005	50
Captan	0.1	0.0023	0.00007	100
DDD	<4	0.34	<0.4	---
Pentachlorophenol	<730	0.013	<3	---

[a] Arithmetic mean of population-weighted and seasonally-weighted average personal exposures measured for 173 persons in Jacksonville, FL and 85 persons in Springfield/Chicopee, MA.

[b] Percent of total airborne exposure only, based on outdoor measurements at each home in the two cities.

[c] All risks calculated assuming 70-year lifetime exposure at the measured levels. For banned pesticides, whose environmental concentrations should decrease over time, an alternative calculation of risk (in parentheses) assuming a 10-year half-life in soil is provided.

Table 3. Population-Weighted[a] Concentrations and Standard Errors ($\mu g/m^3$)

Sample type	N	Median	Arith. Mean	Percentile 90%	98%
Daytime PM_{10}					
Personal	171	130 ± 8	150 ± 9	260 ± 12	380
Indoor	169	82 ± 8	95 ± 6	180 ± 11	240
Outdoor	165	83 ± 5	94 ± 6	160 ± 7	240
Overnight PM_{10}					
Personal	168	66 ± 4	77 ± 4	140 ± 10	190
Indoor	163	52 ± 4	63 ± 3	120 ± 5	160
Outdoor	162	74 ± 4	87 ± 4	170 ± 5	210
Daytime $PM_{2.5}$					
Indoor	173	34 ± 4	48 ± 4	100 ± 7	170
Outdoor	167	36 ± 4	49 ± 3	100 ± 6	170
Overnight $PM_{2.5}$					
Indoor	166	26 ± 2	36 ± 2	83 ± 6	120
Outdoor	161	35 ± 2	51 ± 4	120 ± 5	160

[a] Personal samples weighted to represent nonsmoking population of 139,000 Riverside residents aged 10 or above. Indoor-outdoor samples weighted to represent 61,500 homes with at least one nonsmoker aged 10 or above.

Table 4. Major Sources of Emissions Vs Major Sources of Exposure for Pollutants Studied in Total Exposure Studies

	Major Emission Sources	Major Exposure Source
Benzene	Industry; autos	Smoking
Tetrachloroethylene	Dry cleaning shops	Dry-cleaned clothes
Chloroform	Sewage treatment plants	Showers
p-dichlorobenzene	Chemical manufacturing	Air deodorizers
Particles	Industry; autos; home heating	Smoker at home
Carbon monoxide	Autos	Driving; cooking with gas stove

Human Exposure to Airborne Carcinogens/Mutagens: Preliminary Survey on Personal Exposure and Indoor/Outdoor Pollution by Using Highly Sensitive Analytical Methods for PAHs and Nitro-PAHs

Kiyoshi Tanabe
National Institute of Public Health, 4-6-1 Shirokanedai, Minato-ku,
Tokyo 108, Japan
and
Hidetsuru Matsushita
University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

Summary: Methods for micro analysis of PAHs and nitro-PAHs have been developed for direct measurement of personal exposure. Small scale surveys on personal exposure and indoor/outdoor pollution have been carried out by using personal mini-pumps and the developed analytical methods. Information on indoor/outdoor emission sources, activity records, etc. was also collected by questionnaires. The methods/surveys were proved to be useful to investigate human exposure to these genotoxic air pollutants. Atmospheric concentrations, which were largely different day by day and location by location, affected indoor and personal exposure concentrations. Impact of cigarette smoke on personal exposure to PAHs, influence of cooking on PAH concentrations in kitchen, excess exposure to 1-NP on roads and in central city area, etc. were observed. It was also shown that direct measurement of personal exposure is important for accurate evaluation of human exposure.

Introduction

Human exposure to air pollutants cannot be evaluated only based on the results of ambient air monitoring. Indoor pollution by cigarette smoke, NO_2, organic vapors, etc. has drawn attention and has been studied by many researchers[1]. Development of various passive samplers made it possible to carry out personal exposure and indoor pollution surveys on gaseous pollutants without so much difficulties[2-4]. Such surveys combined with questionnaire survey on indoor/outdoor emission sources, activity records, etc. showed many advantages on accurate/detailed evaluation of human exposure including elucidation of pathway/primary factors of exposure, analysis of exposure - lifestyle relationship, characterization of high-risk group, etc.[2-4]

Exposure assessment of airborne carcinogens/mutagens is attracting attention in relation to increase of lung cancer in developed countries. Various studies have been performed on these pollutants in ambient air, stack gas, automobile exhaust, etc. Several studies on indoor pollution by PAHs and nitro-PAHs have also been performed[5-8]. However, it was not easy to carry out personal exposure/indoor pollution survey, which was useful for exposure assessment of gaseous pollutants, because of difficulties both in collection and analysis of personal/indoor samples.

We have developed methods for micro analysis of PAHs and nitro-PAHs by using multicolumn HPLC/spectrofluorometric detection technique to realize direct measurement of personal exposure to these carcinogens/mutagens. Small scale surveys on personal exposure and indoor/outdoor pollution have been carried out by using personal mini-pumps and the developed analytical methods. The methods were sensitive enough to determine these genotoxic chemicals in small amount of particulate samples, and useful information on exposure levels/patterns has been obtained.

Methods

1) Sampling

Personal, indoor and outdoor samples (airborne particulates) were collected on quartz fiber filters by low-noise personal mini-pump (Shibata Scientific Technology Ltd., 1.0 - 1.5*l*/min with constant flow control, alkaline battery/AC100V, 500g including battery, <45dB at 1*l*/min, 100mmH_2O load, 1m distance) for 24 hours. The mini-pump was set in a box for perfect insulation of noise especially during midnight. A laboratory made impactor was used for size selective collection of personal sample (50% cut-off diameter was 2μm). Other samplings without size separation were carried out by using a 25mmϕ open-face filter holder attached with inlet cap which protected a filter and kept air intake speed around 1m/s.

2) Micro analysis of PAHs

A column concentration HPLC/computer controlled spectrofluorometric detection system has been developed for automatic micro analysis of PAHs. A schematic diagram of the system is shown in Figure 1. A sample injected into the system from AS in Figure 1 was conveyed by CH_3CN from pump P1 (0.5ml/min), mixed with H_2O from pump P2 (0.5ml/min) by dynamic mixer M, and concentrated/cleaned-up on concentrator column C within 5min after the injection. After that, valve V was turned to connect column C to separation column S, pump P3 (CH_3CN:H_2O=1:1, 1ml/min) was turned off, flow rates of P1 and P2 were changed to 0.8 and 0.2ml/min, respectively. By these operations, PAHs concentrated on column C were transferred to column S, and separated to each compound. Each PAH was detected by computer controlled spectrofluorometer, of which wavelengths were automatically set/changed by a time program for sensitive and selective detection. After 45min from the injection, HPLC system was returned to the initial condition. Pyrene (Py), benz(a)anthracene (BaA), benzo(k)fluoranthene (BkF), benzo(a)pyrene (BaP), benzo(b)chrysene (BbC), benzo(ghi)pelyrene (BghiP) and dibenzo(a,e)pyrene (dBaeP) were analyzed.

PAHs in particulate samples were extracted to benzene:EtOH=3:1 v/v by ultrasonic agitation, and the solvent was evaporated under N_2 stream and converted to CH_3CN for the HPLC analysis. A constant volume of the sample, usually 300 or 500 μl, was injected at 50min interval into the HPLC system. Determination limits (S/N=10) of PAHs in air were in the range from 0.03ng/m^3 for BaP to 0.1ng/m^3 for dBaeP when 2m^3 of air was sampled by the mini-pump.

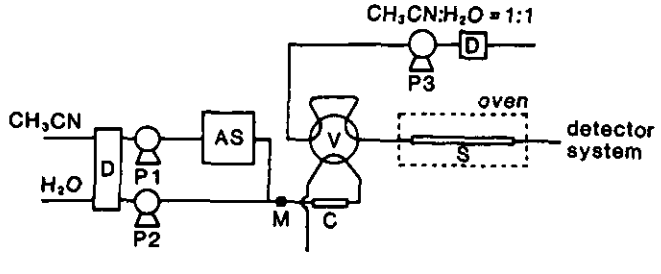


Figure 1. Column concentration HPLC system for automatic micro analysis of PAHs.

P1-P3; HPLC pump, D; degasser, AS; automatic sample injector, V; high pressure valve, M; dynamic mixer, C; concentrator column (4.6mmϕ × 30mm, Kaseisorb ODS-60-5, room temperature), S; separation column (4.6mmϕ × 250mm, ODS-60-5, 40°C)

3) Micro analysis of nitro-PAHs

A multicolumn HPLC/spectrofluorometric detection system has been developed for micro analysis of nitro-PAHs. A schematic diagram of the system and operating condition are shown in Figure 2 and Table 1, respectively. The system consists of 3 main parts, i.e., i) P1, RC and AS for sample injection and for reduction of nitro-PAHs to amino-PAHs, ii) LV, P2, M1, IC and HV for selective concentration of amino-PAHs and sample clean-up, iii) P3, P4, M2, ODS, FL, UV and R for separation and sensitive/selective detection of amino-PAHs. All procedure from the injection/reduction to separation/detection by the 3 parts were performed automatically following the HPLC program shown in Table 1. In the present study, 2-nitrofluorene (2-NF), 3-nitrofluoranthene (3-NFlr), 1-nitropyrene (1-NP), 6-nitrochrysene (6-NC) and 6-nitrobenzo(a)pyrene (6-NBaP) were analyzed.

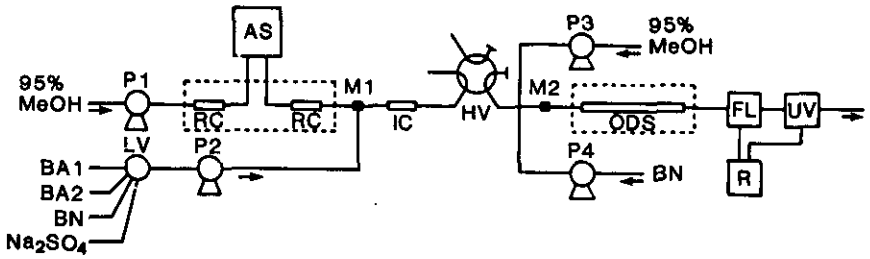


Figure 2. Multicolumn HPLC system for micro analysis of nitro-PAHs.

P1-P4; HPLC pump, LV; buffer selection valve, BA1; McIlvaine buffer (pH2.55, diluted 5 times), BA2; McIlvaine buffer (pH2.55, diluted 10 times), BN; McIlvaine buffer (pH6.00, diluted 2 times), Na_2SO_4; 0.1M Na_2SO_4 solution, AS; automatic sample injector, RC; reduction catalyst column (Pt:Rh=9:1 1% on 5μm alumina, 4mmϕ × 70mm, 80°C), IC; strong cation exchange column (Nucleosil 5SA, 4.6mmϕ × 50mm, room temperature), ODS; ODS column (Nucleosil $7C_{18}$, 4.6mmϕ × 250mm, 60°C), M1,M2; mobile phase mixer, HV; high pressure valve (position 0), FL; spectrofluorometric detector, UV; UV monitor (254nm), R; 2 pen strip chart recorder

Table 1. Operating condition of multicolumn HPLC system.

online reduction/concentration/clean-up

procedure	reduction of nitroarene	concentration of amino-PAHs and sample clean-up	elution of amino-PAHs	reactivation of ion-exchange column	return to the initial condition
pump P1(95%MeOH)	0.32ml/min	0.53ml/min		0.32ml/min	
pump P2(buffer)	0.29ml/min				
buffer change at ion-exchange column	BA1	BA2	BN	Na_2SO_4	BA1
buffer selection by LV	BA1	BA2	BN	Na_2SO_4	BA1

time after injection 0 5 10 15 20 25 30 35 40 45 50min

separation by reversed phase HPLC

procedure	initial condition	introduce amino-PAHs	separation/detection		
position of HV	0	1	0		
pump P3(95%MeOH)	0.53ml/min	0	0.53ml	gradient elution	0.74ml/min
pump P4(buffer)	0.48ml/min	0.19ml/min	0.48ml		0.27ml/min

time after injection 0 5 10 15 20 25 30 35 40 45 50min

Nitro-PAHs in particulate samples were extracted to benzene:EtOH=3:1 v/v by ultrasonic agitation, basic compounds were removed by a liquid-liquid partition with 1N H_2SO_4, and the solvent was evaporated under N_2 stream and converted to CH_3OH for the HPLC analysis. A constant volume of the sample, usually 300 or 500 μl, was injected into the HPLC system. Determination limits of nitro-PAHs in air were in the range from 0.008ng/m^3 for 1-NP to 0.3ng/m^3 for 6-NBaP when 2m^3 of air was sampled by the mini-pump.

Results and Discussions

1) A survey on personal exposure to PAHs (size selective sampling)

A small scale survey on personal exposure to PAHs has been carried out for the evaluation of developed analytical method and to obtain preliminary information on personal exposure level/variation/difference. Personal samples were collected everyday for 7 consecutive days in winter by using the impactors and personal mini-pumps for 3 smokers and 4 non-smokers living in the metropolitan area. Questionnaire was used to obtain information on activity records, smoking and nearby emission sources. Quartz fiber filters for the collection of respirable particulates (<2μm) were replaced everyday, and collection targets for coarse particulates were used throughout the 1 week sampling period.

The methods, i.e., sampling by personal mini-pump and micro PAH analysis by the developed method, were suitable/effective for the survey. PAHs in coarse particulates only accounted for 0.1 - 5.0% of the total PAHs, i.e., most of PAHs were contained in respirable particulates which can deposit on deep part of the lung. It was also suggested that size selective sampling is not always necessary for exposure assessment of PAHs.

Strong correlation was observed among concentrations of PAHs. Personal exposure concentrations were largely different day by day, and extremely high concentrations compared to usual atmospheric PAH levels were observed for smokers, e.g., >10ng/m^3 of BaP for subject 2 (2 days). The daily variation patterns showed good correlation among non-smokers, which suggested that ambient PAH concentrations/variations affect personal exposure concentrations. Weekly average exposure concentrations of BaA, BaP and BghiP were shown in Figure 3. Personal difference in exposure level was examined for BaP (t-test), and the following differences were significant: subject 1 > 4, 5 (level of significance = 90%); 2 > 4, 5, 6, 7

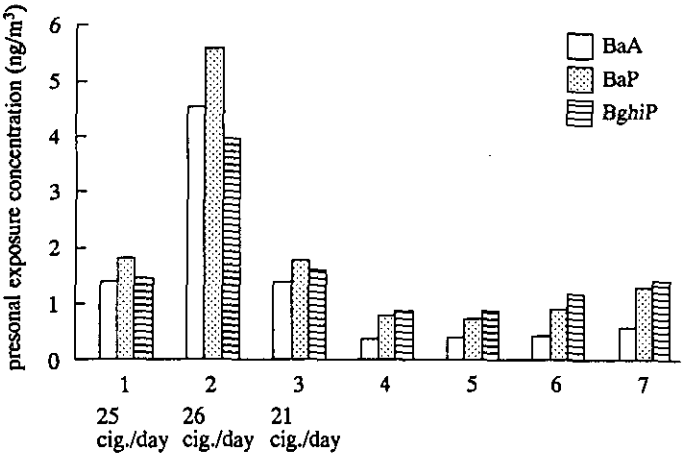


Figure 3. Personal exposure concentrations of BaA, BaP and BghiP

(90%); 3 > 4, 6 (95%), 5 (98%). Three smokers were exposed to high concentration PAHs by passive smoking as well as by active smoking. Apparent factor on exposure other than the cigarette smoke was not observed.

2) A personal exposure and indoor/outdoor pollution survey on PAHs

Following the results of the small scale personal exposure survey, a more extensive survey was carried out to examine the relationship among personal exposure, indoor/outdoor pollution, emission sources, etc. In the survey, personal samples, home environmental samples in kitchen, bedroom and at outdoor were collected everyday for 3 consecutive days in summer and winter for about 20 subjects living in the metropolitan area. Questionnaires were used to get information on indoor/outdoor emission sources, ventilation, smoking, activity records, etc.

PAH concentrations were largely different day by day, and strong correlation was observed among PAHs. Three day average of personal exposure and home environmental concentrations of BaP were shown in Figure 4. Home environmental concentrations were different by subjects

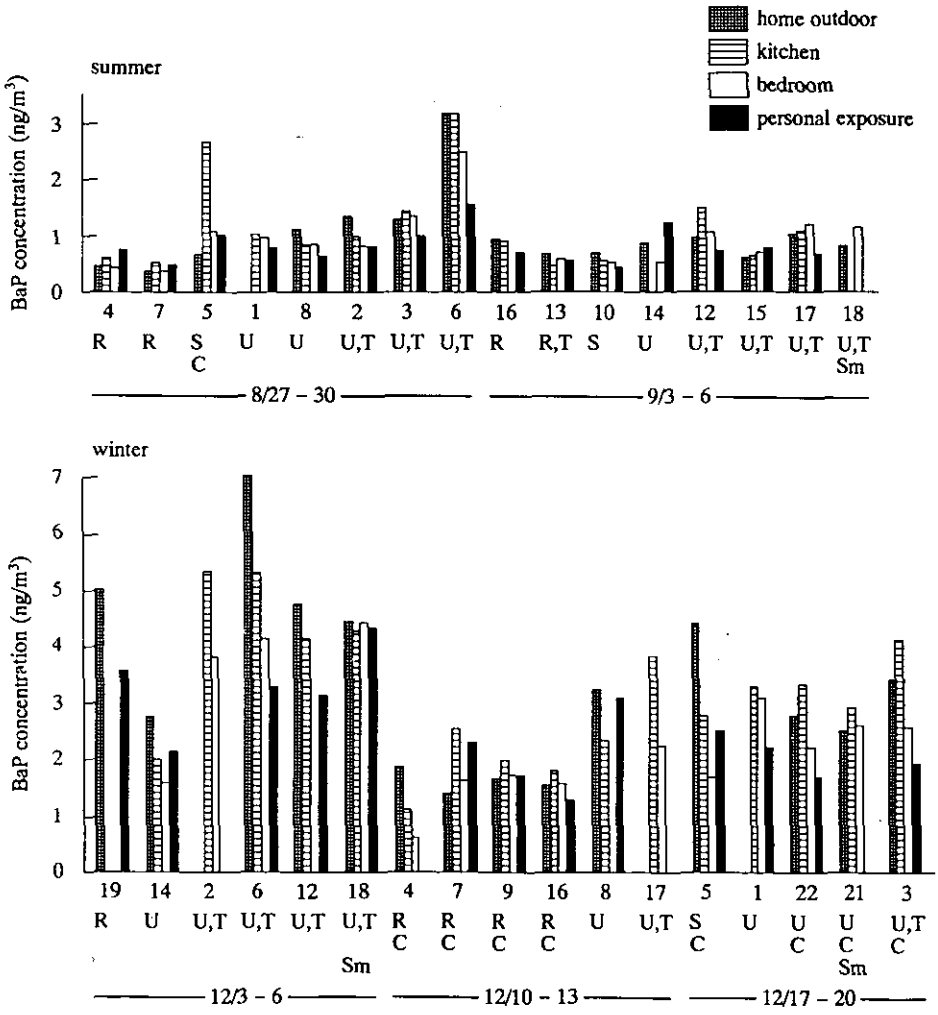


Figure 4. Personal exposure and indoor/outdoor concentrations of BaP

1-22; subject number, R; rural area, S; suburban area, U; urban area, T; nearby traffic (automobile), C; cooking, Sm; smoker

and showed a tendency that they are higher in central city and traffic congested areas. Among home environmental and personal exposure concentrations, strong correlation was observed both in summer and winter, which suggested that ambient air pollution largely affects indoor and personal exposure concentrations. There were only a few smokers among the subjects, and the effect of cigarette smoke was not clear. Influence of cooking was observed in kitchen, however extreme indoor pollution, which was observed in other studies[7,8], was not found.

In summer, overall average concentrations of BaP were 0.99ng/m^3 at home outdoor, 1.06ng/m^3 in kitchen, 0.93ng/m^3 in bedroom and 0.81ng/m^3 for personal exposure. Although the average concentrations were close to each other reflecting good ventilation in the season, significant differences, i.e., kitchen > indoor (95%), personal (98%), outdoor > personal (90%), were found, which suggested the influence of cooking in kitchen. In winter, PAH concentrations were generally higher than those in summer, and overall average concentrations of BaP were 3.39ng/m^3 at home outdoor, 3.10ng/m^3 in kitchen, 2.43ng/m^3 in bedroom and 2.20ng/m^3 for personal exposure. Significant differences were kitchen > indoor, personal (99%); outdoor > kitchen (95%), indoor, personal (99%); indoor > personal (90%). Kitchen and outdoor concentrations were higher than the others. Personal exposure concentration was estimated based on the environmental concentrations and activity records. The estimates and measured values showed good correlation, but significant difference was observed between them (e.g., 15 - 39% difference in winter). It was shown that direct measurement of personal exposure is necessary for accurate evaluation of human exposure to PAHs[9].

3) A personal exposure and indoor/outdoor pollution survey on nitro-PAHs

A personal exposure and indoor/outdoor pollution survey on nitro-PAHs has been carried out to investigate the relationship among personal exposure, indoor/outdoor pollution, emission sources, etc. In the survey, personal samples, home environmental samples in kitchen, bedroom and at outdoor were collected everyday for 3 consecutive days in summer for 10 subjects and in winter for 5 subjects. All subjects were living in the metropolitan area. Questionnaires were used to get information on indoor/outdoor emission sources, ventilation, smoking, activity records, etc. Through the survey, the developed analytical method showed good performances in highly sensitive daily analysis of nitro-PAHs.

Concentrations of 2-NF, 3-NFlr, 6-NC and 6-NBaP were very low. Although the method was sensitive, these nitro-PAHs were below the detection limits for the most of samples, and rarely exceeded 0.1ng/m^3. 1-NP was detected from all samples, and its concentration was largely different day by day and subject by subject. Three day average of personal exposure and home environmental concentrations were shown in Figure 5. Outdoor concentration showed a tendency that it is higher in central city and traffic congested areas. Indoor concentrations were generally lower than outdoor concentration. Except for kitchen of subject 13, there was not apparent indoor pollution by 1-NP. Home environmental concentrations showed strong correlation to each other. Personal exposure concentration also showed good correlation to home environmental concentrations when subjects 5 and 6, who rode bikes back and forth to work (about 2 hours every day), were excluded. Personal exposure concentrations of bike users and subjects living in suburban areas were higher than their home indoor concentrations reflecting excess exposure on roads and in polluted central city area.

Although the surveys in the present study were small scale and the subjects were not selected randomly, they provided good general view on exposure to PAHs and nitro-PAHs. The

methods were proved to be useful for such surveys. Further studies including other pollutants, other environmental media, emission sources, etc. will provide valuable information to prevent exposure to these genotoxic chemicals in the environment.

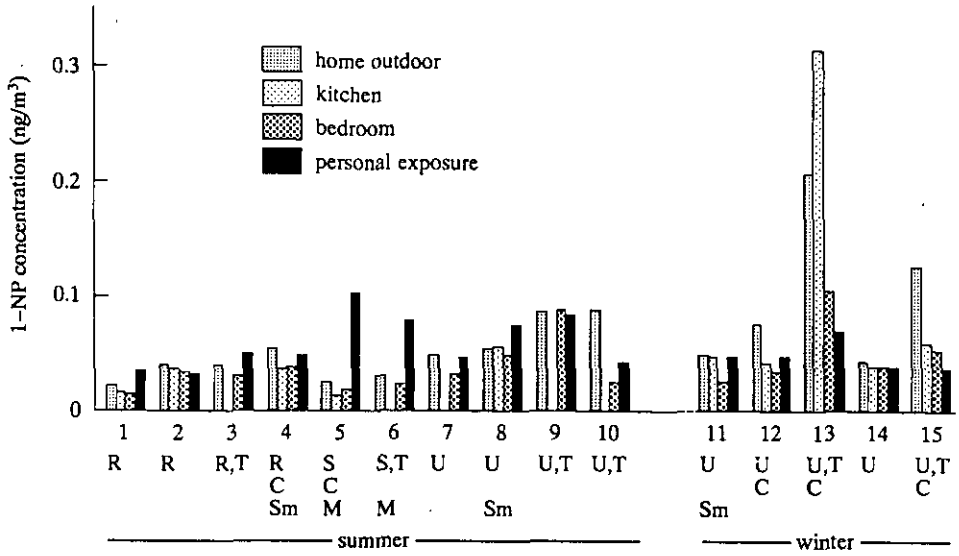


Figure 5. Personal exposure and indoor/outdoor concentrations of 1-NP

1-15; subject number, R; rural area, S; suburban area, U; urban area, T; nearby traffic (automobile), C; cooking, Sm; smoker, M; motorcycle user

References

1) Indoor Air '90. Proc. 5th Internatl. Conf. Indoor Air Quality and Climate. Toronto, Canada (1990).
2) Quackenboss, J. J.; Spengler, J. D.; Kanarek, M. S.; Lets, R.; Duffy, C. P.: Personal exposure to nitrogen dioxide: Relationship to indoor/outdoor air quality and activity patterns. Environ. Sci. Technol. **20**, 775-783 (1986).
3) Matsushita, H.; Tanabe, K.: Exposure monitoring of nitrogen dioxide: an international pilot study within the WHO/UNEP Human Exposure Assesment Locations (HEAL) Programme. Nairobi, WHO and UNEP (1991).
4) Wallace, L. A.: The total exposure assessment methodology (TEAM) study: Summary and analysis. Vol. I. Washington, DC, US Environmental Protection Agency (No. EPA/600/6-87/002a, 1987).
5) Matsushita, H.; Tanabe, K.; Goto, S.: Highly sensitive methods for the evaluation of carcinogens and mutagens indoor. In "Indoor Air Quality" ed. by Kasuga, H. Springer-Verlag, Berlin Heidelberg (1990).
6) Matsushita, H.; Goto, S.; Takagi, Y.; Endo, O.; Tanabe, K.: Human exposure to airborne mutagens indoors and outdoors using mutagenesis and chemical analysis methods. In "Genetic Toxicology of Complex Mixtures" ed. by Waters, M. D. et al. Plenum Press, New York (1990).
7) Suzuki, T.; Saito, Y.; Matsushita, H.; Magara, M.; Sakabe, Y.; Kawamura, T.; et al.: A study on the evaluation of total exposure to carcinogens/mutagens in daily life. In "Annual Report of the 10 Year Strategic Research Project on Cancer" Ministry of Health and Welfare, Tokyo (from 1986 to 1990).
8) Tanabe, K.; Koyano, M.; Matsushita, H.; Kawamura, T.: Indoor PAH concentrations at homes. Proc. 31st Annu. Meet. Japan Soc. Air Pollut. Kanazawa, Japan, pp.471 (1990).
9) Waldman, J. M.; Lioy, P. J.; Greenberg, A.; Butler, J. P.: Analysis of human exposure to benzo(a)pyrene via inhalation and food ingestion in the total human environmental exposure study (THEES). J. Exposure Anal. Environ. Epidemiol. **1**, 193-225 (1991).

Abstract

ROUTES OF EXPOSURE TO POTABLE WATER CONTAMINANTS

Julian B. Andelman
Department of Environmental and Occupational Health
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15261, USA

Traditionally the risks to disease from exposure to contaminants of potable water have been based primarily on direct ingestion of the water. In recent years, however, a growing body of information has indicated that other routes of exposure may be as substantial or more so than direct ingestion, although this is highly agent-specific. Examples are Legionellosis from the inhalation of aerosols from contaminated water and increased risk of lung cancer from volatilized radon. Modeling of dermal transport of chemicals and breath measurements of volatile chemicals following dermal contact with contaminated water indicate that exposures via this route can also be comparable to that of direct ingestion.

Similarly, our laboratory research and measurements in homes have shown that volatilization of chemicals from showers and baths can result in inhalation exposures comparable to those from ingestion. Table 1 is an example based on measurements in bathrooms of two homes using shower water containing 23 and 48 μg/L of trichloroethylene (TCE), respectively. The air in the shower chamber and the bathroom was measured continuously and modeled. Based on the air concentrations, C_a, measured after 6 minutes, the single shower inhalation exposures to TCE in μg, I_c, were shown to vary between 0.7 and 2.4 times that from a typical adult ingestion of the same contaminated water, DWe, also in μg. The inhalation exposures are affected by several factors, including the temperature and flow rate of the water, the type of shower head, the size of and the air flows through the shower chamber and bathroom, and the nature of the volatilizing chemical. In addition, the time of the shower and that spent subsequently in the bathroom are important determinants of exposure.

Two important constants that describe the rate and extent of volatilization are the Henry's law constant, H, and the mass-transfer volatilization coefficient, K. The H constant is the equilibrium ratio of C_a divided by C_w (concentration in water). We use these with the same units, so that H is dimensionless. H depends on water temperature and the nature of the volatilizing chemical. The

dimensionless mass-transfer coefficient, K, is a measure of the fractional extent of volatilization when C_a is zero. K also depends on the nature of the chemical and the temperature, but is highly dependent on the flow regime as well. Table 2 shows the results for measurements of K and the percent volatilization for three chemicals in a full-size shower after 11 minutes, the water temperature being 42-46 °C. It is apparent that the percent volatilization is not a simple function of either H or K. As the concentration of the chemical in the air builds up, it inhibits subsequent volatilization. One can thus conclude that the extent of inhalation exposures in showers and from other indoor water uses will vary considerably with the nature of the chemical and the characteristic of the water use. The surface area of the water plays a key role.

Our indoor air micro-computer model, MAVRIQ (Model for Analysis of Volatiles and Residential Indoor-air Quality), predicts the variation in time of indoor air-concentrations of chemicals volatilized from all water uses, as well as the potential inhalation doses of the inhabitants. The former depends on modeling the water uses, while the latter depends on modeling the location of the inhabitants as well. Figure 1 shows the MAVRIQ predictions of the 24-hour variation in air concentrations in a model home using water containing 20 μg/L of TCE. The highest air concentrations occur in the shower and bathroom. However, substantial air concentrations also occur in other rooms due to point sources in these rooms, as well as the transport of TCE from the rooms containing the point sources.

The MAVRIQ predictions of the cumulative potential inhalation doses are shown in Figure 2 for two adults and a child, all of whom have unique occupancy patterns. Adult 1 is away from the home more than Adult 2 and has a lower potential dose, as do all occupants when the bathroom fan is in operation. It is apparent that such whole-house exposures are highly dependent on the time spent indoors, the nature of the volatilizing chemical, and the characteristics of the water uses in the home, as well as the specific room locations. Because of all of these factors, these potential doses may vary substantially among family members.

These non-ingestion exposures present an additional level of complexity for the regulator in setting risk-based drinking water standards. Also, public health officials responsible for limiting human exposures to hazardous contaminants present in potable water may need to take actions in addition to merely providing alternate drinking water supplies. Information on the relative magnitudes of all routes of exposure, as discussed in this presentation, can assist in such decisions.

REFERENCES

Giardino, NJ, E Gummerman, N Esmen, JB Andelman, CR Wilkes, and MJ Small (1990). Real-time Air Measurements of Trichloroethylene in Domestic Bathrooms Using Contaminated Water. *Proceedings - The Fifth International Conference on Indoor Air Quality and Climate*, Toronto, July 1990, Vol.2, pp 707-712.

Giardino, NJ and JB Andelman (1991). Modeling Volatilization of Chemicals from Showers. Presentation at Annual Conference of American Water Works Association, Philadelphia, PA, June 1991.

Wilkes, CR, MJ Small, JB Andelman, NJ Giardino, and J Marshall (1992). Inhalation Exposure Model for Volatile Chemicals from Indoor Uses of Water. *Atmospheric Environment*, IN PRESS.

Table 1. Comparison of predictions for inhalation exposures from a 6-minute shower versus that from ingestion. From Giardino et al., 1990

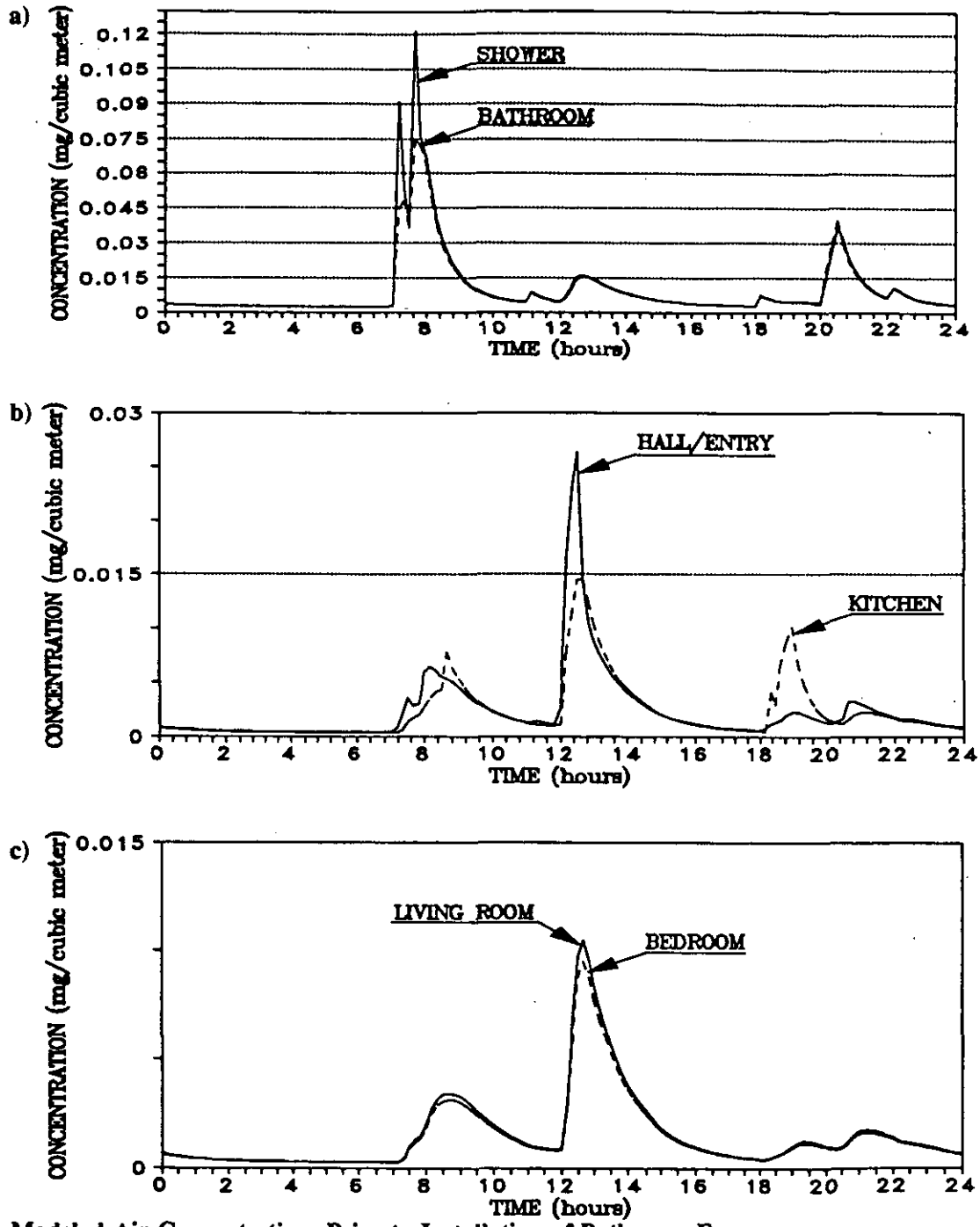
Residence 1	C_s[a] (mg/m3)	I_c[b] (µg)	I_c/DW_c[c]
Measurements from shower	0.55	55	2.4
Model simulation for shower	0.41	41	1.8
Residence 2			
Measurements from shower	0.32	32	0.7
Model simulation for shower	0.78	78	1.6

[a]6-minute average shower-air concentration
[b]Inhalation exposure assuming 1 m^3 per hour breathing rate
[c]Ratio of inhalation exposure to that from ingestion (DW_c) assuming 1 liter of tap water ingested per day

Table 2. Summary of Physicochemical Parameters and Volatilization Measurements in Shower. From Giardino and Andelman, 1991.

Chemical	K	H	Percent Volatilized
TCE	0.79	1.14	81.8
$CHCl_3$	0.59	0.35	56
DBCP	0.65	0.03	22.8

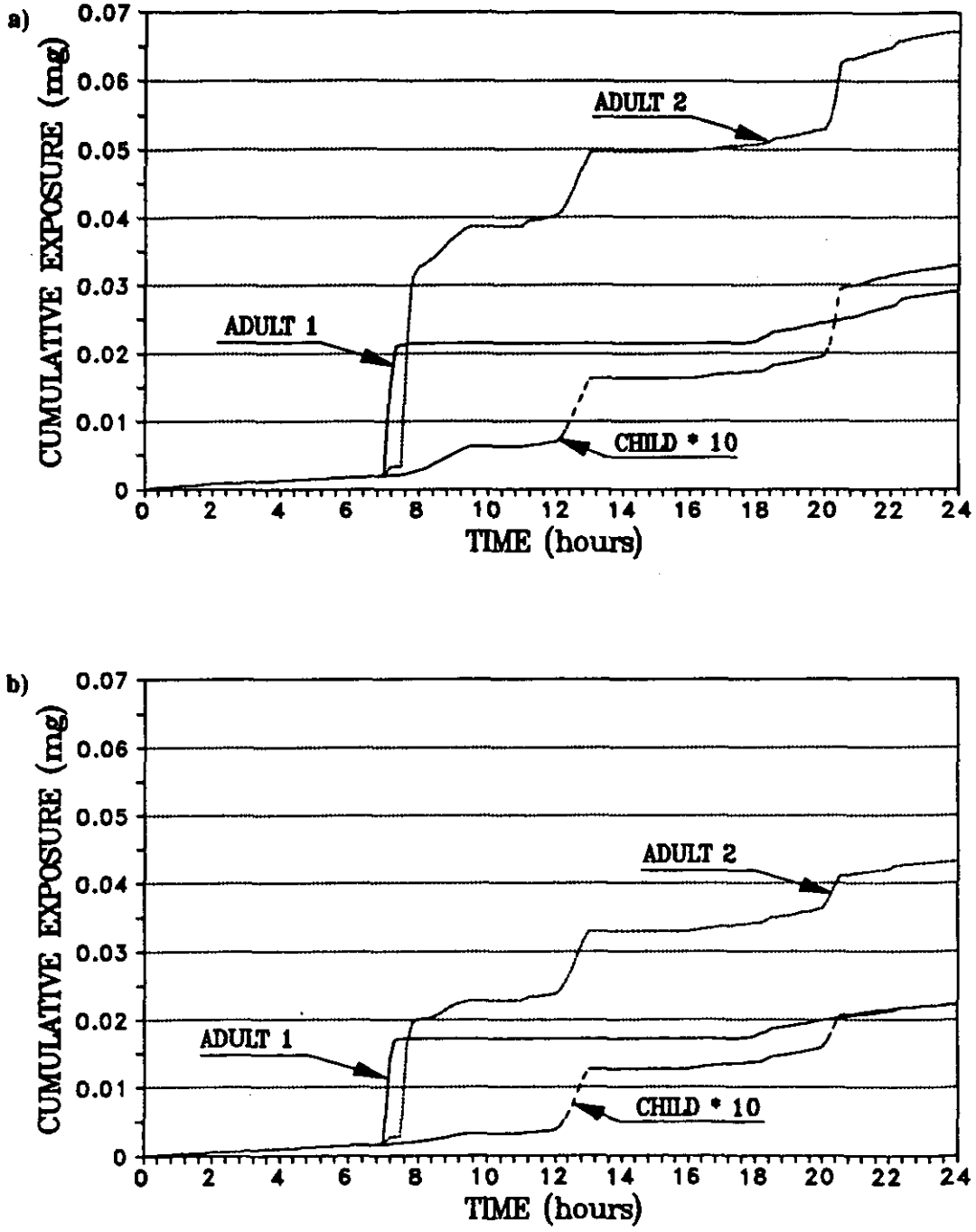
Figure 1. From Wilkes et al., 1992.



Modeled Air Concentrations Prior to Installation of Bathroom Fan.

a) Bathroom and Shower; b) Kitchen and HallNEntry; c) Living Room and Bedroom. (Note the different scales for each)

Figure 2. From Wilkes et al., 1992.



Inhalation Exposures of the Three Occupants.
a) Prior to Installation of the Bathroom Fan; b) After Installation of the Bathroom Fan.

Organotin compounds in coastal biota, Japan

Hiroaki Shiraishi and Yuko Soma
National Institute for Environmental Studies

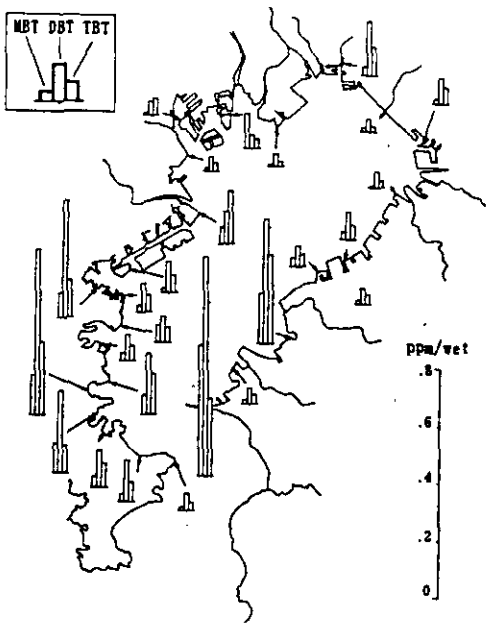
Organotin compounds are used in antifouling paints on boats, ships, docks and nets used in fish farming. Organotin compounds are also toxic to non-target aquatic organisms, particularly to certain mollusks. Tributyltin (TBT) compounds cause thickening of oyster shells, and induce "imposex" (the development of male sex organs in the female) in neograstropods. The TBT concentration in water which initiates these adverse effects is thought to be around 1 ng Sn/L. The contamination of fish by triphenyltin (TPT), which has been used as a cotoxicant with TBT in some antifouling paints, was first noticed by Takami et al. (1988). The Environment Agency of Japan undertook a pilot survey of organotin compounds in the environment. The results showed that TPT concentrations in fish and mussels were higher than TBT concentrations, although the annual production of TPT was about one tenth that of TBT in Japan. The TPT concentration in fish occasionally exceeded the WHO recommendation. Thus, TPT compounds became a Class 2 specified chemical substance (January, 1990) under the "Law concerning Examination and Regulation of Manufacture, etc, of Chemical Substances", which was enacted from 1973, and amended in 1986 to cover recent pollution problems. Class 2 specified chemical substances can be used, produced and imported, but their amounts are asked to report. Because of its toxicity and tendency to accumulate in marine organisms, manufacturers consented to stop the production and sales of TPT formulated antifouling paints in Japan (June, 1989). TBTO (Bistributyltin oxide) became Class 1 in January, 1990 and its use and production was prohibited,

while the other TBT compounds were designated as Class 2 (September, 1990) and still utilized in antifouling paints in Japan.

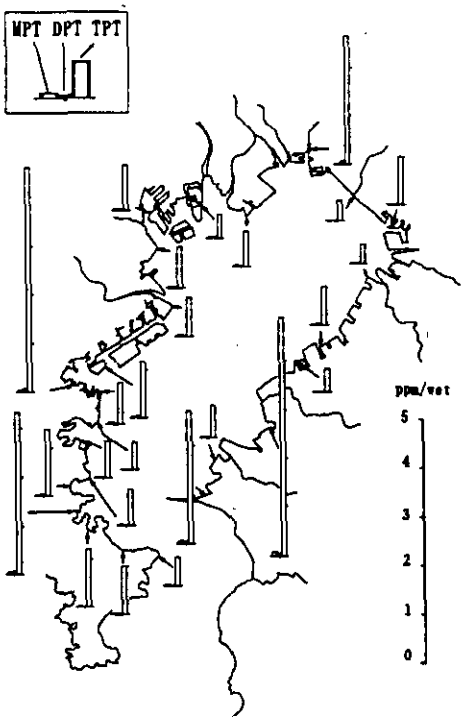
The changes in the concentration of organotin compounds in mussels (*Mytilus edulis*) have been monitored since the restriction of TPT usage. Mussels were collected at two locations in Tokyo Bay from 1989 to 1991. One site was a busy port (Yokohama port), heavily contaminated by organotin compounds, and the other was the river mouth at Urayasu with one tenth the contamination. The TPT concentration in mussels decreased from 4.6 ppm to 0.19 ppm in Yokohama, and from 0.74 ppm to 0.03 ppm in Urayasu. At both sites, TPT was a major phenyltin component, and its degradation products (DPT and MPT) were minor. The phenyltin composition was almost the same and has not changed significantly at either site during the monitoring period. This suggests that the source composition of phenyltins taken by mussels also has not changed significantly, but only that the levels decreased in the order of magnitude. There was no evidence that TPT concentrations in the sediment decreased in the period from 1990 to 1991. The durability of TPT in the sediment and the constancy of phenyltin composition in mussels suggest that the TPT decrease in mussels is chiefly the result of the decrease of the primary TPT input from antifouling paints to the water column rather than from the decrease of the phenyltin redistribution from the sediment. The average half life of TPT in mussels in Tokyo Bay was calculated to be 133 days. The estimated biological half life of TPT in mussels was about 50 days from cultivation studies. Although this value was extrapolated from the short period of cultivation studies (2 to 3 weeks), it can be assessed that metabolic activity of mussels against TPT is weak, and that it takes several months to establish an equilibrium between mussels and sea water. Since the half life of TPT in water is relatively

short, it may be concluded that the extinction rate of TPT in Tokyo Bay water may be equal to or even faster than that of TPT in mussels. The restriction of TPT use found to be effective.

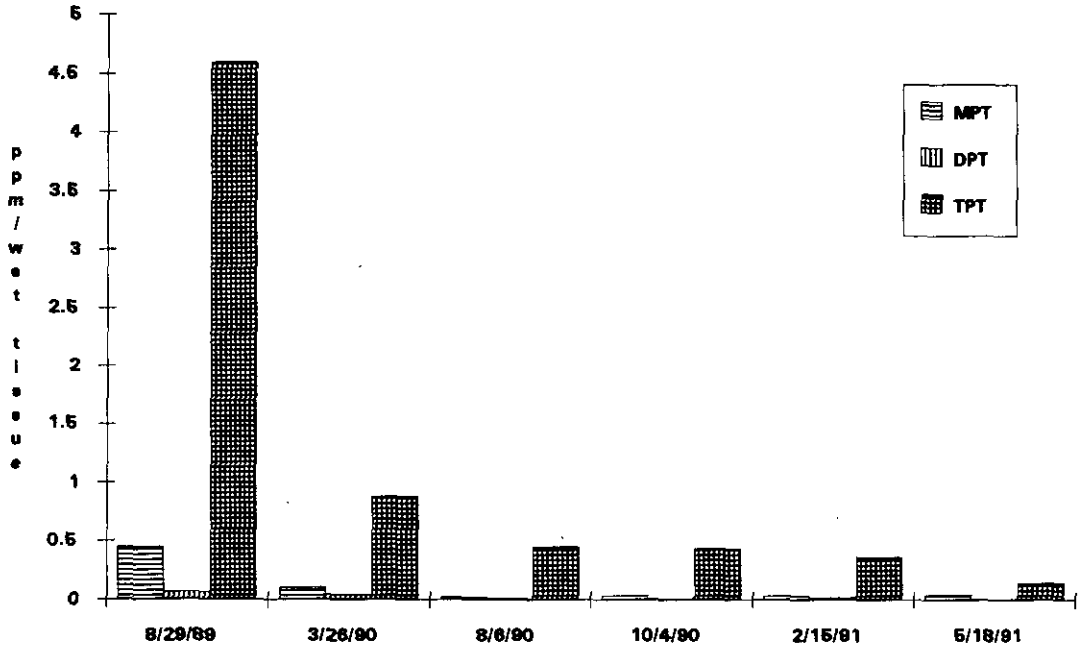
TBT concentrations in mussels showed a large seasonal variation. It was the lowest in summer and the highest in winter. The degradation products of TBT showed the opposite seasonal change to that of TBT, indicating that this seasonal variation was mainly due to the temperature dependence of metabolic activity of mussels. The TBT concentration in mussel was increased with decrease in mussel size. This is also due to limited metabolic activity of small mussel. This study and the other reports showed that there has been no evident reduction in the concentrations of TBT in coastal environment in Japan. Tendency to accumulate TBT seems to be dissimilar among coastal biota, depending upon metabolic activity, habitat, positions in food web, and so on. The concentration of organotin compounds in some coastal biota in Japan will be presented.



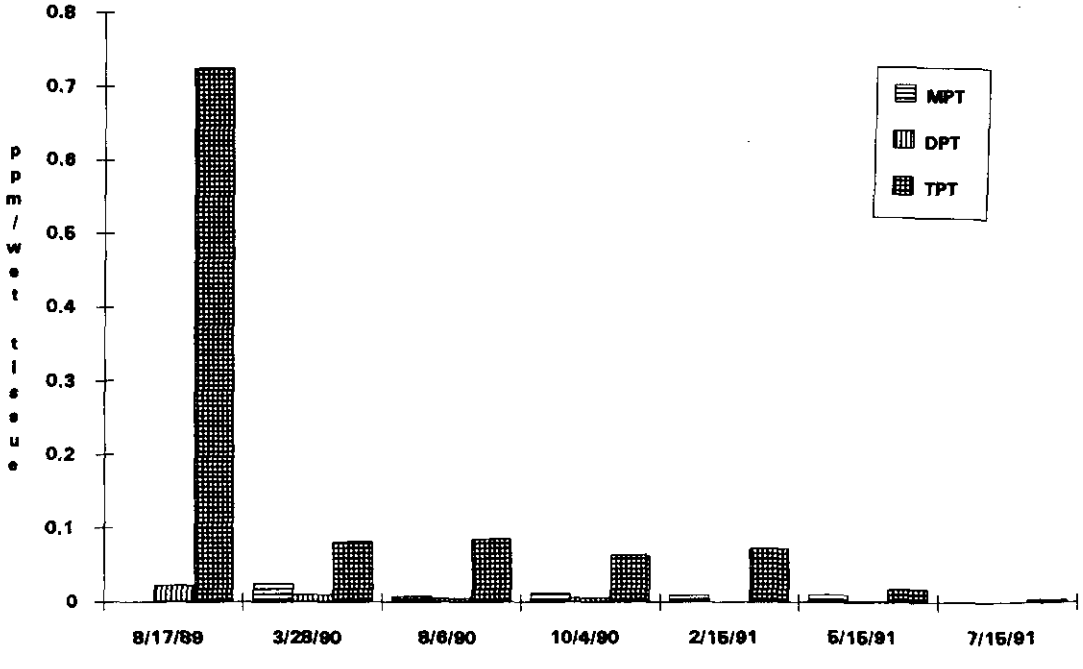
Butyltins (MBT, DBT, TBT) in Tokyo Bay Mussels (August to September, 1989)



Phenyltins (MPT, DPT, TPT) in Tokyo Bay Mussels (August to September, 1989)

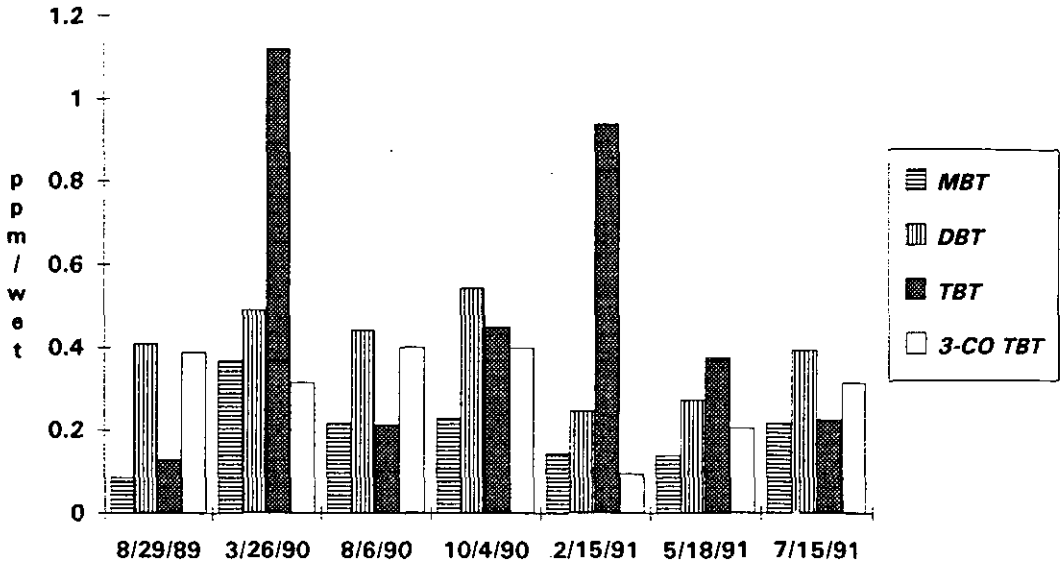


TPT, DPT, and MPT concentrations in mussels collected from Yokohama Port in the period from 1989-1991

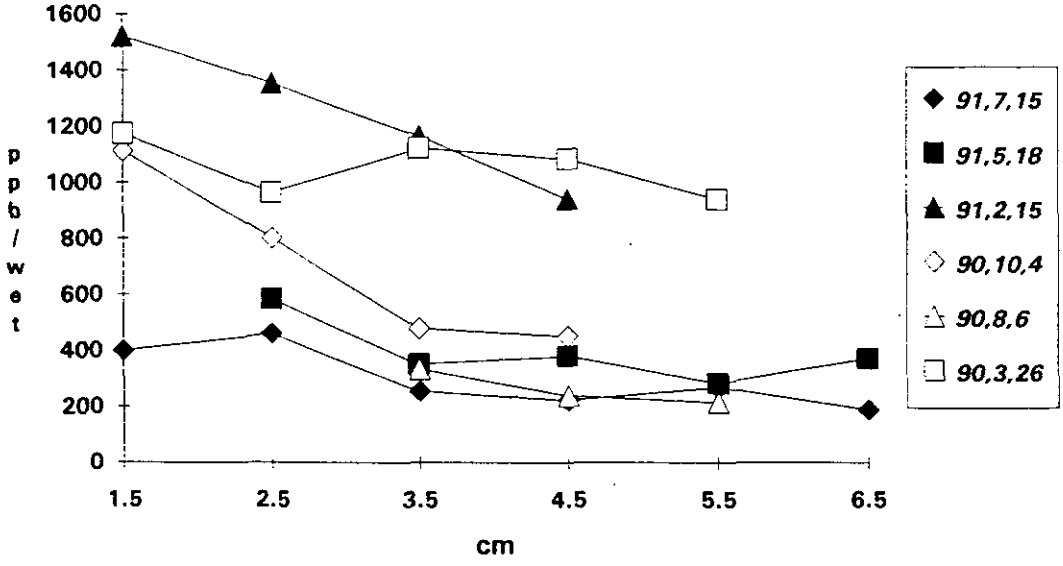


TPT, DPT, and MPT concentrations in mussels collected from Urayasu in the period from 1989-1991

BUTYLTIN CONCENTRATION IN MUSSEL (YOKOHAMA)



TBT CONCENTRATIONS IN MUSSEL (YOKOHAMA)



Session C

Risk Assessment and Risk Characterization

Health Risk Assessment of Monochlorodibenzofuran

Chiharu Tohyama, Seishiro Hirano and Kazuo T. Suzuki
Environmental Health Sciences Division,
National Institute for Environmental Studies,

Summary Trace amounts (1.4 ng/L) of 2CDF were found in tap water distributed in Tsukuba (Shiraishi et al., 1985). Since little is known about the metabolic fate of 2CDF compared to polyCDFs, we have now used not only radiolabeled 2CDF but also 3CDF for a comparative purpose, and investigated the disposition of 2CDF and 3CDF in various organs of rats.

When 2-chloro[^{14}C]dibenzofuran was intravenously administered to the rats, about 86% of radioactivity was found in urine, large intestinal contents and feces within 24 h. Approximately 3% of 2-chlorodibenzofuran (2CDF) radioactivity was present in the adipose tissue 48 h after an intravenous administration. A similar excretion pattern of the compound was observed in orally administered rats. From experiments *in vitro* approximately 80% of 2CDF was present in the red blood cell fraction and the rest in the plasma fraction. Bile cannulation studies revealed involvement of enterohepatic circulation in the metabolism of the compound. Bile specimens that were subjected to enzymatic hydrolysis by arylsulfatase and/or β-glucuronidase showed the presence of various yet unidentified conjugated substances. A comparative study using 3-chlorodibenzofuran (3CDF) showed a similar distribution pattern found in the 2CDF-treated rats, but 2CDF appeared to accumulate more in the adipose tissue and red blood cells. The present study demonstrates that most of 2CDF is quickly metabolized to give rise to a number of metabolites

and excreted from the body, but suggests that the compound once distributed in the adipose tissue may remain there for a relatively long time.

Introduction

Wide-spread environmental contamination due to polychlorinated dibenzofurans (PCDFs) a global environmental issue that draws attentions not only from academia and regulatory authorities but also from the public because the compounds are released into the atmosphere from municipal incinerators and accumulated in the living organisms through the food-web (Kimbrough 1980).

Excessive exposure to PCDFs causes thymic atrophy, and "Yusho" as a most aggravated case, that were reported to occur in Japanese people, in 1968, who ingested rice oil contaminated with these compounds (Kuratsune 1980). Although the predominant contaminant was polychlorinated biphenyls (approximately, 1000 ppm), the PCDFs (approximately, 5 ppm) is now considered to be the cause of the disease (Nagayama et al. 1976 and 1977; Masuda and Yoshimura 1984).

In recent years, trace amounts (1.4 ng/L) of 2CDF were found in tap water distributed in Tsukuba, Ibaraki Prefecture, Japan (Shiraishi et al. 1985). Since no detectable amounts of the compound and its precursors were found in the water of the reservoir, it is speculated that 2CDF was synthesized by the reaction of dibenzofuran, a coating material of tap water pipes, with remaining chlorine ions in the tap water. Less-chlorinated dibenzofurans having the vicinal hydrogen atoms (Morita and Oishi 1977; Rappe et al. 1979; Yoshihara et al. 1981) accumulate less in the liver, and inductions of aryl hydrocarbon hydroxylase and ethoxyresorufin-O-deethylase by 2CDF were not observed in rat

hepatoma cells (Bandiera et al. 1984), suggesting that such trace amounts of 2CDF in the tap water do not exert severe toxic effects on health of the people living in the region. However, 2CDF was found to have very weak mutagenicity in TA98 by Ames assay (Matsumoto et al. 1988) and to induce aniline hydrase and aminopyrine demethylase in the liver of rats treated (ip) at a dose of 100 mg/kg body wt (Saeki et al. 1977)

Since little is known about the metabolic fate of 2CDF compared to more toxic forms of CDFs, such as penta- and hexa-chlorinated compounds (Nagayama et al. 1980; Kuroki et al. 1980; Birnbaum et al. 1980, 1981; Decad et al. 1981a, 1981b; Abraham et al. 1989), probably due to the unavailability of highly purified radiolabeled 2CDF, we have now used not only radiolabeled 2CDF but also 3CDF for a comparative purpose, and investigated the disposition of 2CDF and 3CDF in various organs of rats.

Results

Metabolic Fate of 2CDF in the Body

Changes in tissue levels of 2CDF are summarized in Table 1. Five h after an intravenous injection, approximately 50% of the administered radioactivity was found in the contents of the alimentary tract, urine and feces. Each 40% of the total radioactivity was found in the urine and feces 24 h after injection. After 48 h, these excreta and contents in the small and large intestines accented for 85% of the total administered dose. When radioactivity in the bile was determined, excreted amounts of 2CDF accounted for approximately 60% of the total administered radioactivity by 3 h and leveled off thereafter (Fig. 1). These results suggested the occurrence of enterohepatic circulation.

Regarding elimination of 2CDF from organs at 48 h after the

injection, all the tissues except adipose tissue, blood and gastrointestinal organs, contained 2CDF-derived radioactivity at equal or less than 10% of the level found at 30 min. The adipose tissue and blood had approximately 3% and 0.8% at 48 h, respectively.

In rats which were orally administered with 2CDF, excreted amounts of 2CDF-derived radioactivity were 62.4% and 34.4% in the feces and urine, respectively, by 72 h after the treatment. In the bile-cannulated rats, radioactivity found in the excreta was 13.5% in average after 48 h, which shows that orally administered 2CDF was relatively fast enough to be absorbed through the alimentary tract.

Characterization of Metabolites of 2CDF in the Bile

Figure 2 depicts a separation profile, by a thin-layer chromatography, of 2CDF derived radioactive metabolites in the bile. It was revealed (1) that at least two conjugated compounds either with sulfate or glucuronate are present, (2) that no parent compound of 2CDF was detected in the bile, and (3) that large amounts of polar metabolites other than conjugates with sulfate or glucuronate 2CDF are present.

Metabolic Fate of 3CDF in the Body

Time-course of changes in the contents of 3CDF derived radioactivity is summarized in Table 3. After 5 h after an intravenous injection, 64% of the total radioactivity was found in the large intestinal contents, urine and feces. After 24 h, the cumulative radioactivity found in the urine and feces were 28% and 51%, respectively. By 48 h after the injection, nearly all the radioactivity was detected in the urine, feces, and large

and small intestinal contents. Cumulative amounts of 3CDF derived radioactivity were found to be 51% by 3 h after the intravenous injection, and the excreted amounts of radioactivity into the bile were leveled off by this time (Figure 1). These results suggest that 3CDF and/or the metabolites were subjected to an enterohepatic circulation. At 48 h, it was also found that adipose tissue and blood contained approximately 0.4% and 0.3% of the total radioactivity, respectively. The reason why the cumulative amounts exceeds 100% is probably due to errors in the estimation of relative amounts of skin, muscle, blood and adipose tissue.

Discussion

Since trace amounts of 2CDF were detected in tap water in the area of Tsukuba Science City, the present study was undertaken to obtain fundamental information on risk assessment of the toxicity of this compound. Up to present, a plethora of studies have been carried out on the metabolic fate of CDF chlorinated at more than three positions of the benzene ring. The degrees of general toxicity and carcinogenicity of CDFs are dependent upon both the number and location of the halogen atoms and were found to be higher in the CDFs that are chlorinated at four or five positions of the benzene ring. The biological half-life of the most toxic polychlorinated dibenzofuran, i.e., 2,3,7,8-tetraCDF, is estimated to be 2 days in rats (Birnbaum et al. 1980), 20 days in guinea pigs (Decad et al. 1981a) and 8 days in monkeys (Birnbaum et al. 1981). The half-life of 2,3,4,7,8-pentaCDF and of tetra-, penta- and hexaCDF mixture in mice is also estimated to be 2 - 4 days (Decad *et al.* 1981b) and 2 weeks (Morita and Oishi 1977), respectively. On the whole, the excretion of 2CDF and 3CDF was

rapid, and approximately 80% of each compound was excreted into urine and feces by 24 h. The only difference in retention between 2CDF and 3CDF is that 2CDF tended to remain more in the adipose tissue and whole blood than 3CDF. The partitioning of 2CDF between red blood cells and plasma was found equilibrated with a ratio of 4 to 1 under the present condition, and 2CDF in plasma could be transferred into the cells for further translocation.

The present results from orally-administered rats indicates that 2CDF can be easily excreted since approximately 97% of the total administered dose of 2CDF was found in excreta by 72 h after the administration (Table 2). Studies *in vitro* revealed 2CDF mainly present in red blood cells is translocated to plasma with a ratio of 4 to 1 (Table 3 and 5). In the intravenously administered rats 2CDF excreted into the bile accounted for 60% by 3 h, but that the amounts found in the feces as well as large intestinal contents were only 39% by 5 h, suggesting the possibility that metabolites of 2CDF excreted into the bile is reabsorbed in the small intestine by enterohepatic circulation.

In bile specimens from 2CDF-treated rats, no 2CDF was detected by HPLC. Instead, enzymatic hydrolysis by β-glucuronidase and/or arylsulfatase altered retention times of metabolites, indicating the presence of glucuronic acid conjugates and sulfate conjugates. Additionally, the chemical forms of the conjugates were very complex and other types of metabolites besides the both conjugates were found. A part of the conjugates extractable to ethyl acetate fraction after hydrolysis by the two enzymes, was characterized and identified as 2-chloro-3,7-dihydroxydibenzofuran, 2-chloro-3-hydroxydibenzofuran and 2-chloro-7-hydroxydibenzofuran (Hirano et

al. 1991). Nevertheless, the total yield of these three metabolites was only 8.9%.

According to the result from the Ames test, 3CDF showed stronger mutagenicity than other three isomers of monoCDF (Matsumoto et al. 1988; Matsumoto and Ando 1991). The potency of mutagenicity of 3CDF was about one-fifth in TA98 and about one-twentieth in TA100 of that of benzo[a]pyrene, a positive control. Since the mutagenicity of 3CDF was elevated in the presence of S9 mixture, indicating that metabolic activation has a close association with the mutagenicity. It has been reported that polychlorinated compounds such as 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetraCDF show negative results in the Ames test, but have considerably strong toxicity. As to the induction of cytochrome P-450-dependent monooxygenases, activities of both aryl hydrocarbon hydroxylase and 7-ethoxycoumarin-O-deethylase were found increased predominantly by 3CDF and slightly by 2CDF in cell lines derived from rat hepatoma (H4-II-E-C3) and human Chang liver (Miura and Takahashi 1990). These data suggest that, among monoCDF isomers, a chlorine position 3 is more important not only in terms of the mutagenicity but also the induction of drug metabolizing enzyme system. It should be described that the induction of these enzymes by 2CDF was nearly comparable to one twentieth the concentration of dexamethasone, a control steroid used in the same assay.

The mechanism of toxicity of CDFs has not been clarified. However, induction of aryl hydrocarbon hydroxylase correlates with the toxicity of the CDFs, and is used as a marker for toxicity. Poland and coworkers (1976) reported that the biological potency (induction of the enzyme) of CDFs relative to

2,3,7,8-tetrachlorodibenzodioxins has a extremely wide range; for instance, 2,3,7,8-tetraCDF is rated 67, and 2,8-CDF, 2,3-CDF and dibenzofuran are all considered inactive (9.4×10^{-7}). Although the biological potency of monoCDFs are not listed in the result, it would be reasonable to consider that the potency of 2CDF and 3CDF will be minimal in the assay system. In addition to these results, because of the rapid metabolism and elimination and very weak mutagenicity of 2CDF, as well as very low concentration of 2CDF in the drinking water, it could be allowable to conclude that daily intake of the water in Tsukuba area would not cause serious health effects.

Acknowledgment

We thank Dr. Masatoshi Morita (National Institute for Environmental Studies) for a gift of pure 2-CDF and 3-CDF.

References (papers written by researchers of NIES only)

Hirano S, Tohyama C, Mitsumori F, Ito H, Suzuki KT (1991) Identification of metabolites of 2-Cllorodibenzofuran in the rat. Arch Environ Contam Toxicol 20: 67-72

Matsumoto M, Ando M, Ohta Y (1988) Mutagenicity of monochlorodibenzofurans detected in the environment. Toxicol Lett 40: 21-28

Matsumoto M, Ando M (1991) Mutagenicity of 3-chlorodibenzofuran and its metabolic activation. Environ Molecular Mutagenesis 17: 104-111

Miura T, Takahashi Y (1990) The induction by monochlorodibenzofuran isomers of xenobiotic metabolizing systems in cell lines derived from rat and human hepatoma. Toxicol In Vitro 4: 185-192

Morita M, Oishi S (1977) Clearance and tissue distribution of

polychlorinated dibenzofurans in mice. Bull Environ Contam Toxicol 18: 61-66

Shiraishi H, Pilkington NH, Otsuki A, Fuwa K (1985) Occurrence of chlorinated polynuclear aromatic hydrocarbons in tap water. Environ Sci Technol 19: 585-590

Tohyama C, Hirano S, Suzuki KT (1992) Disposition and Excretion of 2-Chlorodibenzofuran in the Rat. Arch Environ Contam Toxicol (in press)

Table 1 Tissue distribution of ^{14}C-2-chlorodibenzofuran-derived radioactivity in rats[a]

Tissue	Time after administration			
	30 min	5 h	24 h	48 h
Adipose tissue	13.2 ± 3.5	9.65 ± 4.38	3.87 ± 0.54	2.87 ± 1.96
Adrenal gland	0.03 ± 0.01	0.003± 0.002	0.003± 0.000	0.003± 0.003
Cerebellum	0.08 ± 0.03	0.004± 0.001	0.001± 0.000	0.001± 0.001
Cerebrum	0.35 ± 0.18	0.02 ± 0.01	0.005± 0.002	0.006± 0.004
Heart	0.19 ± 0.04	0.10 ± 0.12	0.01 ± 0.00	0.01 ± 0.01
Kidney	1.82 ± 0.35	0.67 ± 0.25	0.13 ± 0.04	0.09 ± 0.05
Large intestine	0.33 ± 0.06	2.64 ± 3.12	0.18 ± 0.09	0.10 ± 0.11
Large intestine contents(LIC)	0.11 ± 0.02	33.7 ± 2.2	7.88 ± 5.66	5.88 ± 8.22
Liver	10.6 ± 1.2	2.79 ± 0.34	1.04 ± 0.15	0.76 ± 0.19
Lung	0.22 ± 0.03	0.06 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
Muscle	10.8 ± 3.5	2.42 ± 1.55	0.72 ± 0.17	0.73 ± 0.52
Pancreas	0.23 ± 0.07	0.08 ± 0.06	0.01 ± 0.00	0.01 ± 0.01
Skin	23.8 ± 3.5	5.08 ± 0.57	0.67 ± 0.18	0.60 ± 0.46
Small intestine	6.48 ± 2.61	1.99 ± 0.37	0.24 ± 0.11	0.13 ± 0.10
Small intestine contents	12.1 ± 3.1	15.5 ± 1.3	1.70 ± 0.38	1.23 ± 1.29
Spleen	0.09 ± 0.02	0.02 ± 0.01	0.01 ± 0.00	0.01 ± 0.00
Stomach	0.28 ± 0.08	0.08 ± 0.07	0.04 ± 0.03	0.02 ± 0.02
Testis	0.38 ± 0.11	0.09 ± 0.05	0.03 ± 0.01	0.02 ± 0.02
Thymus	0.22 ± 0.11	0.01 ± 0.00	0.005± 0.002	0.004± 0.002
Whole blood	4.98 ± 0.29	1.97 ± 0.37	0.67 ± 0.22	0.81 ± 0.47
Feces[b](F)	−[c] −[c]	5.54 ± 9.59	40.6 ± 7.0	38.5 ±11.2
Urine[b]	0.43[d] −	10.9 ± 9.5	38.3 ± 2.6	40.5 ± 4.5
LIC+F[b]	0.11 ± 0.02	39.2 ±10.6	48.3 ± 1.5	44.4 ± 3.1
Sum total	86.6 ± 3.8	93.4 ±12.7	96.1 ± 4.0	92.4 ± 1.6

a. Rats were intravenously injected with ^{14}C-2-chlorodibenzofuran at a dose of 87.5μg DBF/rat (12.8μCi/rat). The unit is expressed as a percentage of total dose per each organ or tissue, and values are mean ± SD for 3 rats.

b. Values indicate cumulative excreted amounts of ^{14}C-2-chlorodibenzofuran-derived radioactivity.

c. No feces were excreted during the observation period.

d. Urine was collected from the bladder of two rats.

Table 2 Excreted amounts of ^{14}C-2-chlorodibenzofuran-derived radioactivity in rats[a]

Tissue	Time after administration			
	24 h	48 h	72 h	Cumulative amounts[b]
Urine	28.2 ± 1.6	5.7 ± 1.9	0.5 ± 0.1	34.4 ± 1.6
Feces	45.5 ± 5.2	14.2 ± 3.2	2.6 ± 0.4	62.4 ± 3.1
Urine + Feces	73.7 ± 5.9	20.0 ± 4.6	3.1 ± 0.4	96.8 ± 1.8

a. Rats were orally administered with ^{14}C-2-chlorodibenzofuran at a dose of 87.5μg DBF/rat (12.8 μCi/rat). The unit is expressed as a percentage of total dose per each organ or tissue, and values are mean ± SD for 4 rats.

b. Values indicate cumulative excreted amounts of ^{14}C-3-chlorodibenzofuran-derived radioactivity up to 72 h after the administrations.

Table 3 Tissue distribution of ^{14}C-3-chlorodibenzofuran-derived radioactivity in rats[a]

Tissue	Time after administration			
	30 min	5 h	24 h	48 h
Adipose tissue	11.5 ± 3.7	10.9 ± 1.3	2.43 ± 1.00	0.36 ± 0.08
Adrenal gland	0.016± 0.008	0.004± 0.001	0.001± 0.001	0.001± 0.000
Cerebellum	0.056± 0.016	0.005± 0.002	0.003± 0.001	0.002± 0.001
Cerebrum	0.23 ± 0.11	0.019± 0.002	0.029± 0.038	0.009± 0.004
Heart	0.14 ± 0.01	0.300± 0.006	0.010± 0.001	0.006± 0.001
Kidney	5.05 ± 0.58	1.64 ± 0.46	0.14 ± 0.02	0.058± 0.005
Large intestine	0.27 ± 0.06	1.89 ± 0.54	0.40 ± 0.17	0.137± 0.145
Large intestine contents(LIC)	0.11 ± 0.02	40.6 ± 2.6	3.50 ± 0.55	0.40 ± 0.15
Liver	16.7 ± 1.6	3.60 ± 0.70	1.09 ± 0.11	0.67 ± 0.06
Lung	0.29 ± 0.04	0.076± 0.023	0.021± 0.002	0.011± 0.001
Muscle	9.91 ± 1.55	3.10 ± 1.75	0.66 ± 0.11	0.56 ± 0.08
Pancreas	0.31 ± 0.08	0.038± 0.012	0.010± 0.003	0.009± 0.003
Skin	15.8 ± 4.5	3.87 ± 1.4	0.76 ± 0.31	0.35 ± 0.08
Small intestine	7.78 ± 0.81	1.65 ± 0.15	0.23 ± 0.11	0.079± 0.032
Small intestine contents	20.8 ± 4.7	12.9 ± 1.7	1.59 ± 0.66	0.36 ± 0.07
Spleen	0.073± 0.014	0.020± 0.003	0.009± 0.001	0.006± 0.001
Stomach	0.24 ± 0.02	0.049± 0.023	0.014± 0.001	0.021± 0.017
Testis	0.34 ± 0.09	0.068± 0.015	0.025± 0.011	0.018± 0.004
Thymus	0.082± 0.025	0.012± 0.002	0.003± 0.001	0.003 (2)
Whole blood	5.91 ± 0.26	1.37 ± 0.23	0.42 ± 0.07	0.28 ± 0.08
Feces[b](F)	—[c] —[c]	—[c] —[c]	50.7 ± 2.5	51.1 ± 2.6
Urine[b]	0.77 (1)	23.2 ± 7.8	28.2 ±14.1	52.2 ± 2.4
LIC+F[b]	0.11 ± 0.02	40.6 ± 2.6	54.2 ± 3.0	51.5 ± 2.4
Sum total	95.8 ± 6.5	105.0 ± 6.8	90.3 ± 9.7	106.7 ± 0.4

a. Rats were intravenously injected with ^{14}C-3-chlorodibenzofuran at a dose of 87.7μg DBF/rat (11.7 μCi/rat). The unit is expressed as a percentage of total dose per each organ or tissue, and values are mean ± SD for 3 rats.

b. Values indicate cumulative excreted amounts of ^{14}C-3-chlorodibenzofuran-derived radioactivity.

c. No feces were excreted during the observation period.

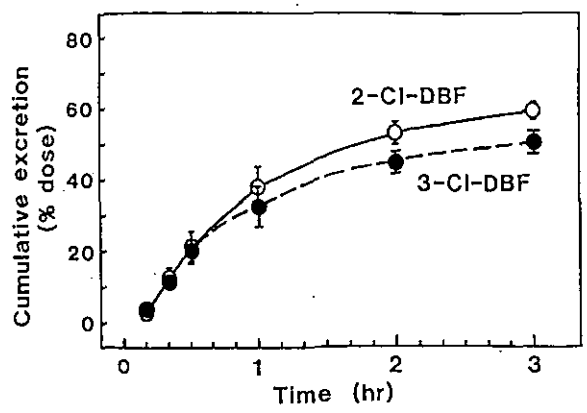


Fig. 1 Cumulative excreted amounts of radioactivity of ^{14}C in the bile from rats treated with either ^{14}C-2-chlorodibenzofuran or ^{14}C-3-chlorodibenzofuran. Points and bars indicate mean ± SD for 3 to 4 rats.

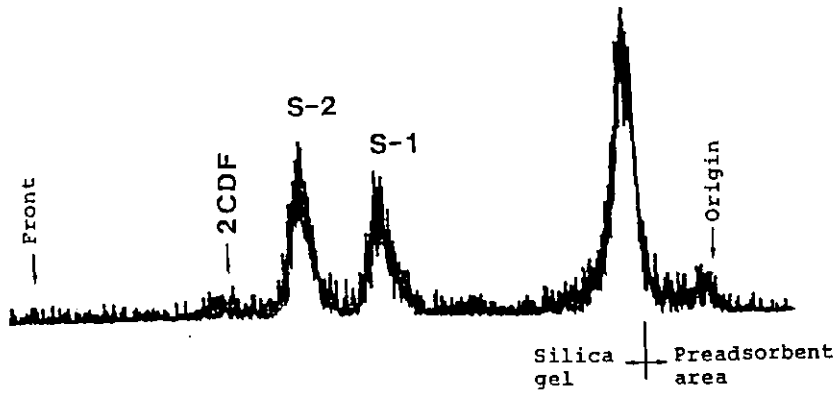


Fig. 2 Radiochromatogram of the 2-chlorodibenzofuran metabolites separated by TLC

Enzymatically treated bile fluid was extracted in ethyl acetate, applied to a TLC (slica gel) plate and developed with the solvent (benzene: methanol=4:1). The radioactivity on the TLC plate was analyzed by a radiochromatoscanner. Two peaks(S-1 and S-2) were developed on the TLC plate with the solvent. 2-chlodibenzofuran (2CDF) was developed at Rf level of 0.68.

HEALTH RISK ASSESSMENT OF DIOXIN AND RELATED COMPOUNDS: CONSIDERATION OF THE MECHANISM OF TOXICITY.

Thomas A. Gasiewicz, Environmental Health Science Center, The University of Rochester School of Medicine, Rochester, New York, USA, 14642.

The halogenated aromatic hydrocarbons represent a group of structurally related compounds which include the halogenated dibenzo-*p*-dioxins, dibenzofurans, azo- and azoxybenzenes, and certain biphenyls, terphenyls, and naphthalenes. They have received considerable attention as environmental contaminants due to numerous accidental poisonings of both human and animal populations, and their extreme toxic potency in experimental animals. Of primary concern has been the ability of these compounds to produce reproductive, immunologic and neoplastic effects. Additional findings that certain of these are environmentally ubiquitous and persistent has prompted many governmental agencies worldwide to evaluate the possible human health risks posed by them, estimate acceptable exposures, and regulate their production and use based on these estimations. However, the extrapolation procedures employed and the subsequent recommendations from these agencies have varied considerably due mainly to the assumptions used. The lack of consistency among these agencies has contributed to public confusion and has precluded a unified effort for an effective regulation of these compounds.

Within the past 15-20 years very basic research has yielded considerable information related to the molecular mechanisms by which 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and its analogs and congeners act. This and further knowledge will facilitate a scientifically-based approach to risk assessment by giving credence to assumptions used in estimating acceptable exposures and the risks associated with these exposures. This paper will review the current knowledge on the mechanism of action of the halogenated aromatic hydrocarbons, and indicate if and how this knowledge may influence the assumptions made in approaching risk assessment.

One of the first investigated effects of TCDD was the induction of cytochrome P450IA1 (CYPIA1) and its associated mono-oxygenase activities, one of which is aryl hydrocarbon hydroxylase (AHH). The rank-order induction of this activity by congeners

of TCDD followed a defined structure-activity relationship. These data were consistent with the existence of a specific macromolecule, or receptor, which is able to transduce a ligand-elicited signal to result in altered expression of the structural gene for CYPIA1 . Additional work using inbred strains of mice defined the *Ah* locus which designates the trait of responsiveness for induction of CYPIA1 by ***a***ryl ***h***ydrocarbons. Finally, in 1976 Alan Poland and coworkers identified a protein in hepatic cytosol that bound TCDD and its congeners with high affinity and specificity. The relative binding affinity of these congeners to this protein matched their ability to induce AHH activity in the whole animal. Furthermore, the relative presence or absence of detectable high affinity receptor in different mouse strains was associated with their relative responsiveness to AHH induction by TCDD or its congeners. Similar studies using mouse hepatoma cell lines are consistent with these data. These studies provided evidence that the induction of CYPIA1 by TCDD was mediated by its specific binding to the Ah receptor (AhR).

Subsequent studies by a variety of investigators have shown that the TCDD· receptor complex is in fact a gene regulatory protein which binds directly to specific oligonucleotide enhancer sequences located upstream of the CYPIA1 structural gene, and increases the transcription of this gene. Alpha-naphthoflavone, a TCDD antagonist, competes with TCDD for receptor binding and blocks the ability of the receptor to interact with these specific DNA sequences, thus corroborating the relationship between AhR presence and its function. Presumably, the mechanism by which TCDD modifies the expression of a variety of other genes is similar, although to date only a few of these have been identified to be directly controlled by the receptor.

Similarly, all data to date imply that the toxicity of the halogenated aromatic hydrocarbons is mediated by the binding of these compounds to the AhR and the modulation of gene expression. The relative binding affinities of TCDD and its congeners correlate with their rank-order potencies to produce a variety of toxic responses. Secondly, the ability to evoke these toxic responses in various inbred strains of mice segregates with the the presence of the *Ah*-responsive (Ah^b) allele and the presence of the high affinity receptor. There is in some cases, a correspondence between the ontogeny of the presence and amount of AhR and whole-animal target organ specificity. In teratogenicity studies,

this has been shown by a temporal correlation between the ontogeny of AhR in mouse embryonic palate and the elicitation of cleft palate following dosing of pregnant females with TCDD and structural analogs.

The available information to date is consistent with the notion that the extreme potency of TCDD as a carcinogen is due to its ability to act as a tumor promoter by enhancing the neoplastic expression of otherwise initiated cells. Furthermore, the structure-activity relationship for tumor promotion and the genetic segregation of promotion indicates that TCDD and its congeners act through the AhR.

Thus, the data are consistent with a model in which the binding of TCDD or any other agonist to the AhR initiates transformation of this protein to a form that has high affinity for DNA. Once bound to specific DNA acceptor sites, transcription (or repression) of regulatory and structural genes is initiated. The resulting messenger RNAs are translated into proteins, some of which have been identified, and include CYPIA1. However, there are likely many others that have not been identified and may be involved in specific TCDD-elicited toxic responses.

If, based on the above evidence, we take the simplest assumption that binding of TCDD and its congeners to the AhR represents the initial and rate-limiting step in the series of events which lead to the ultimate toxic responses, then we may be able to use classical pharmacology to explain the action of these chemicals as a function of ligand·receptor binding. Using the law of mass action, the magnitude of a response (effect, E) will be directly proportional to the occupancy of the AhR (here R) by an agonist or ligand (L), with a maximal response (E_{max}) corresponding to occupancy of all the receptors. Thus,

$$L + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} LR \qquad E$$

and,

$$\frac{E_L}{E_{max}} = \frac{[LR]}{R_T} = \frac{[L]}{K_D + [L]}$$

where

$$K_D = \frac{[L]\,[R]}{[LR]} = \frac{k_{-1}}{k_1}$$

is the affinity of ligand binding, the equilibrium dissociation constant, R_T is the total number of receptors, and E_L represents the response at some ligand concentration. One half the maximal response or

$$\frac{E_L}{E_{max}} = 0.5$$

occurs at the ligand concentration equivalent to the K_D value, and here $E_L = ED_{50}$. The log dose-response curve defined by these relationships is sigmoidal with the initial phase showing little change in binding or response over a substantial increase in ligand concentration. Importantly, the law of mass action states that at very low doses there is no threshold response. Therefore, low dose risk estimates using a linearlized multistage model cannot be rejected simply on the basis of the mechanism of action of TCDD being receptor mediated and making the assumptions built into the law of mass action.

It is clear however, that the present data base is inadequate to support all of the assumptions involved in this simple receptor model, and in fact, more recent data indicate that modifications of this model are appropriate. It is intuitively apparent that the more the ultimate biological response is removed from the initial interaction of ligand with the AhR, the more complicated might be the relationship between occupancy and the final response. Thus, the final response might be represented as a series of coupled events initiated by TCDD binding to the AhR. Any one of these events may be rate limiting and/or involve a cooperative, threshold, or irreversible interaction. For these cases, the ED_{50} value for a particular response may be much greater than the K_D for ligand binding to the receptor and the shape of the dose-response curve may be very different than the ligand binding curve. For example, recent data indicate that prior to DNA binding the ligand-bound AhR must undergo a transformation step involving its interaction with another protein (P) to form a transcriptionally active heterodimer complex. Thus,

$$LR + P \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} LR \cdot P$$

Furthermore, the transformed AhR complex, LR·P, must bind to DNA in a sequence-specific manner, and thus,

$$LR\text{-}P + DNA \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} LR \cdot P \cdot DNA$$

The exact kinetics of these events have yet to be determined. In addition, the relative concentrations of R, P, and available DNA containing the appropriate sequence may be tissue specific. Research has also shown that, at least in the liver, there are "spare" Ah receptors, i.e., only a small percentage of the total number of available receptor sites need to be occupied for sustained maximal enzyme induction. Considering that AhR concentration in different tissues may vary by two orders of magnitude, it is possible that TCDD may be a full agonist in a tissue with high receptor concentrations but only be a partial agonist in a tissue where the receptor concentration is much lower. With respect to DNA binding, data are already available which indicates that there are at least four regions upstream of the transcription start site for the CYPIA1 gene. Although, each site can interact independently with the transformed AhR, the relative rate of gene transcription may be dependent upon cooperative interactions between these sites as well as a number of additional tissue-specific transcription factors. Therefore, the events initiated by ligand binding to the AhR and culminating in altered gene transcription likely involves a series of tissue-specific and complex, but well regulated, interactions.

Within the next few years we will likely have enough data to kinetically describe the events initiated by TCDD binding to the AhR and leading to the transcription of a particular gene. However, for toxicological outcomes such as altered immune responses and cancer, where multiple steps and regulatory processes are involved, and where, in most cases, we do not yet know what altered gene or genes determine the particular toxic responses, the task of defining and understanding all of the indivivual events involved becomes much more difficult. Furthermore, the modulation of some genes by TCDD may not be a direct

result of AhR binding to the upstream enhancer element for that particular gene. For many of these cases, it may be necessary to empirically determine the dose-respose relationships using a combination of whole animal studies and assessment of tissues from humans exposed to these compounds. Here, again it is important to recognize that although a particular response may be AhR-mediated and may involve as an intermediate step the transcriptional activation (or repression) of a particular structural gene by the AhR, the exact concentration-occupancy and dose-response relationships for these early events may not necessarily be the same as for the final response since subsequent critical steps may involve rate-limiting cooperative, threshold, and/or irreversible interactions. For example, recent data from Dr. Lucier's laboratory suggests that the proportion of liver occupied by preneoplastic foci in an initiation-promotion model did not increase until CYPIA1 induction by TCDD was maximal. This implies that some threshold event is involved in TCDD-induced liver tumor promotion. In addition, the ED_{50} values for a variety of toxic responses elicited by TCDD are usually much higher than for the induction of AHH activity, again implying that a complex series of coupled events is involved in signal transduction. These relationships become even more complex and difficult to model if one considers the likelihood that tissue-specific factors and/or hormonal interactions may influence tumor promotion. For example, while intact ovaries appear to be necessary for the hepatocarcinogenic actions of TCDD in the rat, ovariectomy increases the incidence of diethylnitrosamine-initiated and TCDD-promoted lung tumors in this species.

Receptor theory is largely based on equilibrium processes and does not provide information related to chronic exposures. Furthermore, it does not allow for consideration of the pharmacokinetic differences among TCDD analogs and congeners, or for changes in receptor concentrations with time. This information is important since the tissue concentration of TCDD necessary for AhR binding and elicitation of steps leading to a biological response are likely to be time-dependent. The incorporation of physiologically based pharmacokinetic models will likely prove to be extremely useful in providing a quantitative description of the dynamic processes affecting AhR-mediated events.

Thus, it is likely, and in some cases there are sufficient data to indicate, that multistep processes are involved in AhR actions that lead to the final biological

consquences. It follows then that it becomes unreasonable to strictly assume that 1) K_D values representing halogenated aromatic hydrocarbon binding affinities for the AhR closely reflect ED_{50} values for a particular toxicological response, 2) that the shape of the dose-response curve for any response will closely resemble that for ligand binding, and 3) that the shape of these curves for different responses will be similar.

Despite the qualifications in the use of receptor theory for approaching the risk assessment of the dioxins and related compounds, the finding that the mechanism of these compounds involves receptor binding as the first step in the process leading to toxicological consequences represents, for a number of reasons, an extremely important step in both estimating a relative risk of these compounds and outlining a method of approach for refining this risk assessment. 1) The receptor model implies a reversible and non-threshold relationship. This distinguishes it from one-hit models of mutagenic agents such as radiation or alkylating chemicals (although DNA repair processes likely introduce nonlinearities into a one-hit model). However, reversible reactions may have persistent consequences and we do not yet know whether in fact all the subsequent events leading to a toxic responses initiated by TCDD, such as carcinogenesis, are reversible. 2) The receptor binding model has been, and will continue to be, an extremely useful tool to estimate the relative toxicity of the various analogs and congeners of TCDD, and to identify antagonists and their actions. 3) The model provides a rational basis for the extrapolation of animal results to humans. The properties of Ah receptor proteins in experimental animals and humans are similar. Likewise, recent data suggest that the dose-response relationships for at least some effects are similar in experimental animals and humans. 4) The model provides some basis for determining sensitive human sub-populations. Functional polymorphisms in the receptor have been observed in mice and rats, and recent data suggest this to be the case in humans. Studies in mice also suggest that having a particular genotype may make an animal more susceptible to TCDD-elicited tumor promotion. 5) Knowing the theory and limitations of the receptor model allows us, as researchers, to focus on experimental designs to obtain data useful for the purposes of risk assessment. 6) Finally, and perhaps more importantly at this time, knowing the K_D value for ligand binding allows for a conservative approximation of an allowable tissue concentration of

TCDD below which there is a low probability for toxic consequences. However, the recommendation of an exposure limit should also be made in consideration of the occupancy of the receptor produced by background exposures to TCDD and its analogs and congeners. Depending on where the background occupancy is on the binding curve, any additional exposure above this background may or may not result in a significant increase in additional occupancy and perceived health risk.

In summary, the data available are consistent with a model in which the events leading to the toxic effects of the halogenated aromatic hydrocarbons are initiated by their binding to the AhR. This information provides both a useful model for making a conservative estimate of the relative risk of these compounds and further outlining a method of approach for refining this risk assessment

Estimation of Toxic Dose of Atmospheric Compounds in Japan

Takashi Miura*,Kiyoshi Tanabe**, Yuko Soma*

(*The National Institute for Environmental Studies, **Institute of Public Helath)

Recent trends of atmospheric pollution in Japan show characteristics of urbanization. The amounts of nitrogen dioxide and suspended particulate matter rose in urban areas, primarily due to automobile exhaust, and polluted areas extended to the outskirts of large cities. In addition, various kinds of organic compounds have been detected in urban atmosphere, though each is small in quantity, and, however, pollutions are rapidly extending to the rural areas. It is therefore important to assess health effects of atmospheric organic compounds not under control. In this report we present the results of health risk assessment of 13 organic compounds detected in Japanese atmospheres in combination with the known health risks of those chemicals.

Concentrations of organic compounds in the Japanese atmospheres:

In order to clarify exposure levels of organic compounds results of atmospheric surveys were collected mainly from survays performed by Environment Agency and regional governments in Japan and average concentrations in each areas were calculated. The number of average con-

centrations obtained was 142 to 26. The average concentrations were divided into five classes according to the population size in each areas. By this procedure the number of average concentrations was equilibrated. Fortunately, there is little bias observed among areas surveyd. So far as concerned with chlorinated hydrocarbons, such as trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane, there are highly significant correlations between the average concentration and population size showing emission from artificial sources. The average concentration of benzene also was higher as the population size increased (Table 1).

On the other hand, carbon tetrachloride showed different pattern resulting in little clear population dependency (Table 2). This type of chemicals includes chloroform and 1,2-dichloroethane.

Table 3 shows the average concentrations of 13 organic compounds of the atmosphere in Japan.

Estimation of health risks of atmospheric chemicals:

In order to clarify health risks of atmospheric chemicals, results of animal inhalation experiment were collected. Cancer risks were calculated by using a Toxirisk. To extrapolate animal data to human, the following factors were adapted: human life-span 70 years, body weight 70 kg, and breathing volume 20 m^3/day.

As shown in Table 4, excess cancer risk for benzene was highest and amounted to 66 per 10^6. More than 10 excess cancer risks per 10^6 was carbon tetrachchloride and tetrachloroethylene. Excess cancer risks in

cities with a population of more than one million were 2.7- and 1.4-fold higher than the total average for tetrachloroethylene and benzene, respectively. On the other hand, such higher excess cancer risks were not observed in dichloromethane and 1,2-dichloroethane.

The non-cancer health risks of 10 organic compounds was calculat from NOAELs of animal inhalation experiments.

In order to extrapolate animal data to human, the same factors as adapted in the case of cancer risks were used. Uncertainty factors were as follows; extrapolation from animal to human 10 and human to sensitive human 10. As shpown in Table 5, the ratio of NOAEL to exposure concentration was lowest in benzene, 10 for the total average concentration and 8 for the average concentration of large cities. The ratio was less than 100 in carbon tetrachloride. Remaining seven compounds showed the ratio exceeding 1000.

In conclusion, chronic health effects of 13 organic compounds detected in the atmosphere in Japan were assessed by using risk assessment methodologies. Among them, benzene was revealed to be the most risky in both cancer and non-cancer health risks. Attention should be paied to carbon tetrachloride and tetrachloroethylene in the case of cancer risks and cabon tetrachloride and toluene in the case of non-cancer health risks. These approaches will be helpful to set priorities for risk management, although there remain many problems to be disolved in risk assessment methodologies.

Table 1. The Concentration of Atmospheric Benzene in Japan

Population ($x10^4$)	Number of data	Number of areas	Concentration ($\mu g/m^3$)		
			Mean*	Max.	Min.
>100	21	6	11.5 (13.1)	30.7	4.5
30～100	15	8	7.9 (9.2)	18.9	2.3
10～ 30	11	5	6.8 (9.2)	23.7	1.3
3～ 10	17	10	6.5 (9.2)	23.7	1.3
<3	2	2	6.1 (6.1)	6.1	6.1
Total	66	31	8.2 (10.3)	30.7	1.3

*Geometric mean (arithmetical mean)

Table 2. The Concentration of Atmospheric Carbon Tetrachloride in Japan

Population ($x10^4$)	Number of data	Number of areas	Concentration ($\mu g/m^3$)		
			Mean*	Max.	Min.
>100	36	8	0.88 (1.22)	8.80	0.28
30～100	11	4	0.82 (1.08)	4.57	0.44
10～ 30	7	4	0.96 (1.10)	2.45	0.44
3～ 10	25	11	0.57 (0.59)	1.27	0.30
<3	31	16	0.58 (0.74)	3.25	0.07
Total	110	43	0.71 (0.92)	8.80	0.07

*Geometric mean (arithmetical mean)

Table 3. The Concentration of Organic Compounds in Japanese Atmosphere

	Concentration(μg/m^3)			Exposure Level(μg/day)		
	mean(1)*	mean(2)**	Range	mean(1)*	mean(2)**	Range
benzene	8.2	11.5	1.28～30.72	164	229	26～614
toluene	17.7	33.9	1.88～84.95	353	677	38～1,695
o-xylene	3.4	5.2	0.44～14.79	69	104	9～296
m-xylene	4.8	8.4	0.44～20.88	96	169	9～418
p-xylene	2.3	3.6	0.44～ 8.70	45	72	9～176
p-dichlorobenzene	0.4	1.5	0.02～ 5.20	8	30	0.4～104
dichloromethane	0.7	1.5	0.05～ 7.02	14	30	1～140
chloroform	0.6	0.8	0.10～21.31	12	16	2～426
carbon tetrachloride	0.7	0.9	0.07～ 8.80	14	18	1～176
1,2-dichloroethane	0.2	0.3	0.01～23.09	4	5	0.2～462
1,1,1-trichloroethane	1.8	3.1	0.03～37.00	36	62	0.6～740
trichloroethylene	1.0	2.4	0.08～31.68	21	49	2～634
tetrachloroethylene	1.0	2.7	0.05～39.00	20	54	1～780

*The total geometric mean, **The geometric mean of cities with a population of more than one million

Table 4. Estimation of Cancer Risks by Organic Compounds in the Atmosphere

	Concentration ($\mu g/m^3$)		Unit Risk $(\mu g/m^3)^{-1}$ (IRIS)	Excess Risk per10^6	IARC ranking	Ref.
benzene	Mean(1)	8.22	8.0×10^{-6} (8.3×10^{-6})	66	A	
	Mean(2)	11.46		92		Maltoni et al.'83
carbon tetrachloride	Mean(1)	0.71	6.8×10^{-5} (1.5×10^{-5})	48	2B	Bioassay
	Mean(2)	0.88		60		Center'86
tetrachloroethylene	Mean(1)	1.00	1.0×10^{-5} (pending)	10	2B	NIH '78
	Mean(2)	2.68		27		
dichloromethane	Mean(1)	0.68	3.0×10^{-6} (4.1×10^{-6})	5	2B	Duuren'89
	Mean(2)	1.51		2		
trichloroethylene	Mean(1)	1.04	8.8×10^{-7} (withdrawn)	1	3	Maltoni et al.'86
	Mean(2)	2.43		2		Fukuda et al.'83

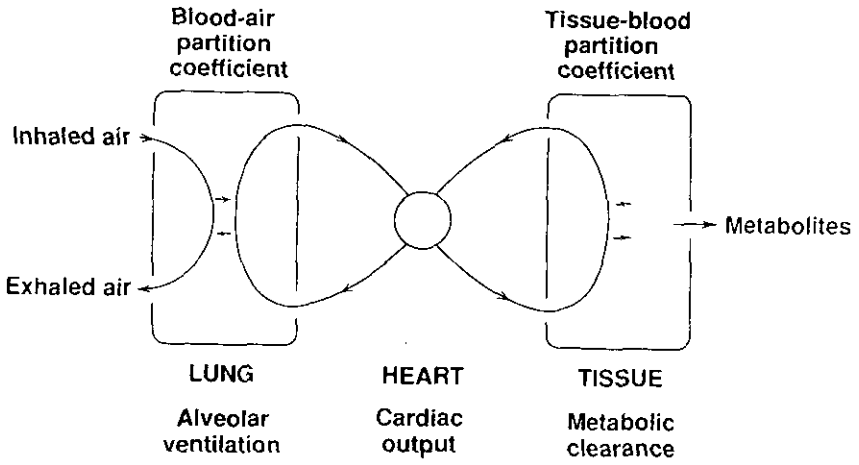
Table 5. Estimation of Non-Cancer Health Risks by Organic Compounds in the Atmosphere

	Exposure Level(A) ($mg/20m^3/day$)	NOAEL(B) (mg/70kg/day)	B Ax10x10	Ref.
bensene	Mean(1) 0.164	172	10	Deicham et al.'63
	Mean(2) 0.229	hematology	8	
carbon tetrachloride	Mean(1) 0.014	113	81	Bioassay
	Mean(2) 0.018	liver	63	Center'86
toluene	Mean(1) 0.353	4,039	114	CIIT '80
	Mean(2) 0.677	hematology	60	
o-xylene	Mean(1) 0.069	1,603	232	Jenkins et al.'70
	Mean(2) 0.104	growth	154	
1,2-dichloroethane	Mean(1) 0.004	518	1,295	Hofman et al.'71
	Mean(2) 0.005	liver, kidney	1,036	
p-dichlorobenzene	Mean(1) 0.008	1,337	1,671	Loesr & Litchfield'83
	Mean(2) 0.030	liver, kidney	446	
1,1,1-trichloroethane	Mean(1) 0.036	6,300	1,750	Quast et al.'84
	Mean(2) 0.062	growth	1,016	

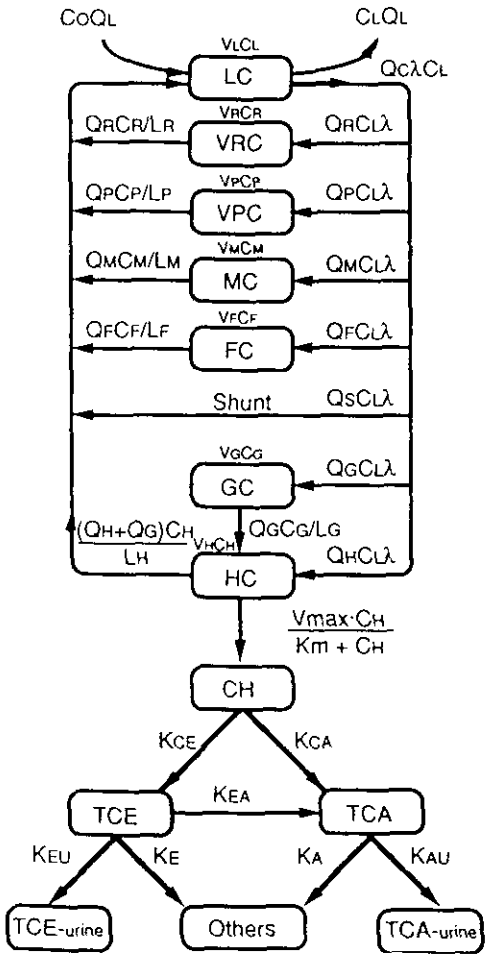
TOXICOKINETICS OF TRICHLOROETHYLENE IN THE WORKPLACE

AKIO SATO
Department of Environmental Health, Medical University of Yamanashi, Tamaho, Yamanashi, 409-38 Japan

Slide 1



Factors which affect the transfer of solvent vapors in a living body.



Slide 2

A physiological pharmacokinetic model for trichloroethylene.
LC = lung compartment; VRC = vessel-rich compartment; VPC = vessel-poor compartment; MC = muscle compartment; FC = fat compartment; GC = gastrointestinal compartment; HC = hepatic compartment. C = concentration in mg/L; V = volume of compartment in L; Q = flow in L/min; L = tissue/blood partition coefficient; λ = blood/air partition coefficient. Subscripts denote the following: O = inhaled air; C = cardiac output; L = LC; R = VRC; P = VPC; M = MC; F = FC; G = GC; H = HC. CH stands for chloral hydrate; TCA for trichloroacetic acid; TCE for trichloroethanol. The rate constants apply as follows: K_{CE}, CH to TCE; K_{CA}, CH to TCA; K_{EA}, TCE to TCA; K_{EU}, urinary TCE excretion; K_{AU}, urinary TCA excretion; K_E, TCE elimination through other routes; K_A, TCA elimination through other routes.

Slide 3

MODEL DESCRIPTION

COMPARTMENT	FLOW % OF Qc (flow)	VOLUME % OF Body (vol)	PARTITION tissue:blood (lambda)	INIT C mg/l (Co)
Lung	100	V1	-	0.00
Richly	37.9	2.99	3.42	
Poorly	6.3	8.46	1.64	
Muscle	11.4	41.48	1.64	
Fat	5.3	21.13	68.00	
Shunt	15.1	-	-	
GI	17.1	1.90	2.99	
Liver	6.9	2.34	4.40	
Blood			9.50	
Qc (l/min)	5.17			
Km			2.50	
Vmax			3.20	
Ql	Qc			
bw (Kg)		61.40		

Control panel

Co	0.544
start	0
stop	7200
mindt	0.01
maxdt	0.20
incr	1.01
interval	100
simtime	7201.53
row	78
dt	0.20

Results

time	Co	Clung	Cblood	Xtce
0.429	0.54	0.113	1.1075	0.092
2.113	0.54	0.14	1.3905	3.486
3.796	0.54	0.149	1.4726	12.12
4.013	0.54	0.149	1.4784	13.61
		136	0.3709	16.73
		111	0.1154	29.05
		105	0.048	40.83
		103	0.0257	51.82
		102	0.018	61.97
		102	0.0163	66.70
		101	0.0145	75.68
		101	0.0136	83.96
		101	0.0131	91.57
		101	0.0127	98.59
		101	0.0123	105.0
		101	0.012	111.0

Figure 4. The spreadsheet: "model description," "control panel," and "results."

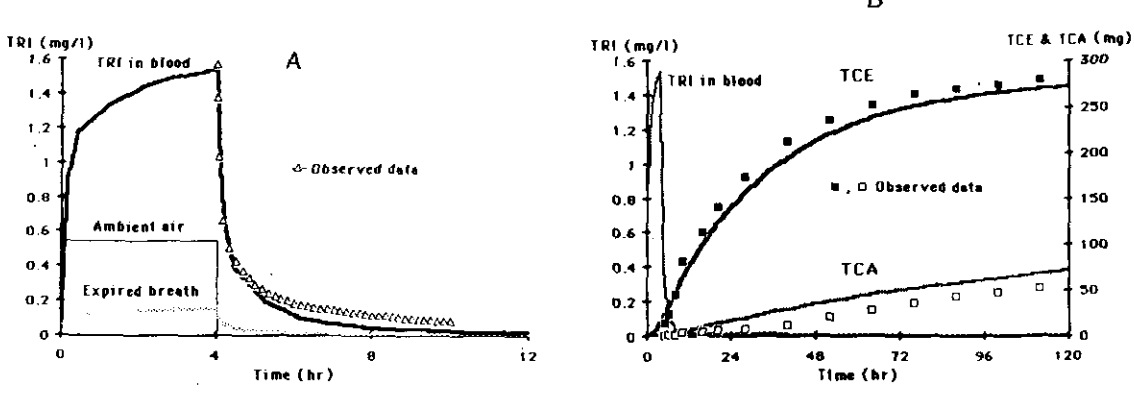
Slide 4

TABLE 2. Parameters Used in the Simulation Model

Compartment	Volume, L[A]	Blood Flow[A] (L/min)[A]	Partition Coefficient
Lung	V_L[B]	Q_C[C]	
Richly perfused	0.030BW[D]	$0.379Q_C$	3.42
Poorly perfused	0.085BW	$0.063Q_C$	1.64
Muscle	0.415BW	$0.114Q_C$	1.64
Fat	0.211BW	$0.053Q_C$	68.00
Gastrointestinal	0.019BW	$0.171Q_C$	2.99
Liver	0.023BW	$0.069Q_C$	4.40
Shunt		$0.151Q_C$	
λ (blood/air partition coefficient)		9.92	
V_{max}, mg/min[E]		$0.17\ (BW)^{0.7}$	
K_m, mg/L[E]		2.5	
Q_L		Q_C	

[A]From Davis et al.[11]
[B]V_L = functional residual capacity + 1/3 of tidal volume + volume of arterial blood × λ + volume of lung tissue × lung/air partition coefficient.[12]
[C]$Q_C = 0.25(BW)^{0.74}$ (from Guyton[13]).
[D]BW = body weight in kg.
[E]From Koizumi.[14]

Slide 5



Comparison between simulated and experimentally observed curves. A, trichloroethylene (TRI) concentration in blood; B, urinary excretion of TCA and TCE. The observed data were from an experimental exposure where four male volunteers (61.4 kg on average) inhaled 100 ppm trichloroethylene for 4 hours.

Slide 6

EXTERNAL AND INTERNAL DOSES FOR INHALED CHEMICALS

External dose = level of exposure

Airborne concentration

Airborne concentration x time

Time-weighted average (TWA) concentration

Internal dose = dose in a strict sense (the amount of chemical that has effectively entered the body)

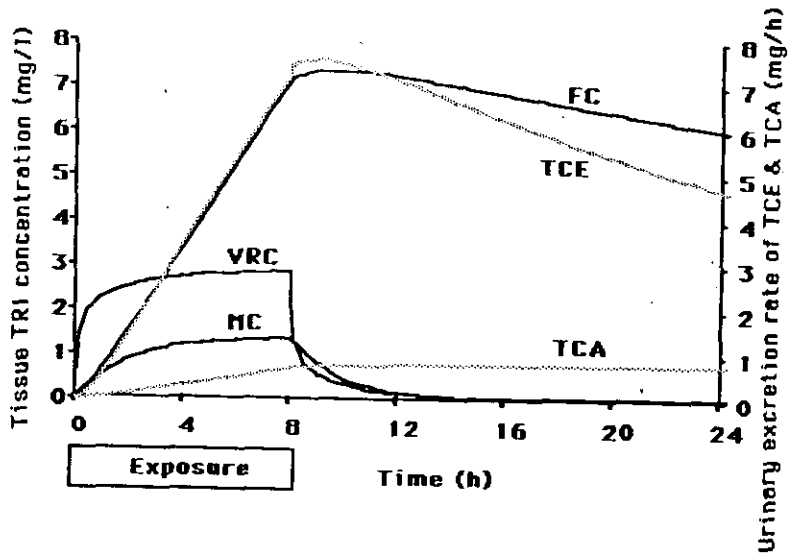
Concentration in tissues

Concentration in tissues x time

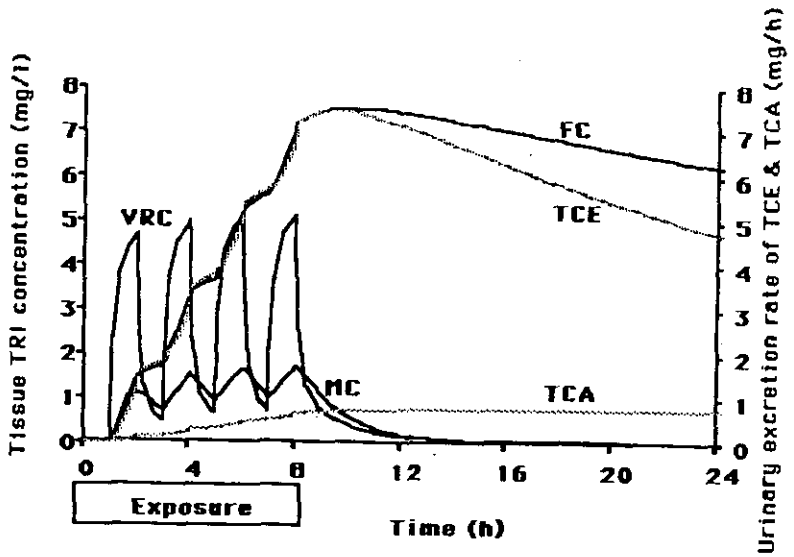
Metabolite concentration in tissues

Metabolite concentration in tissues x time

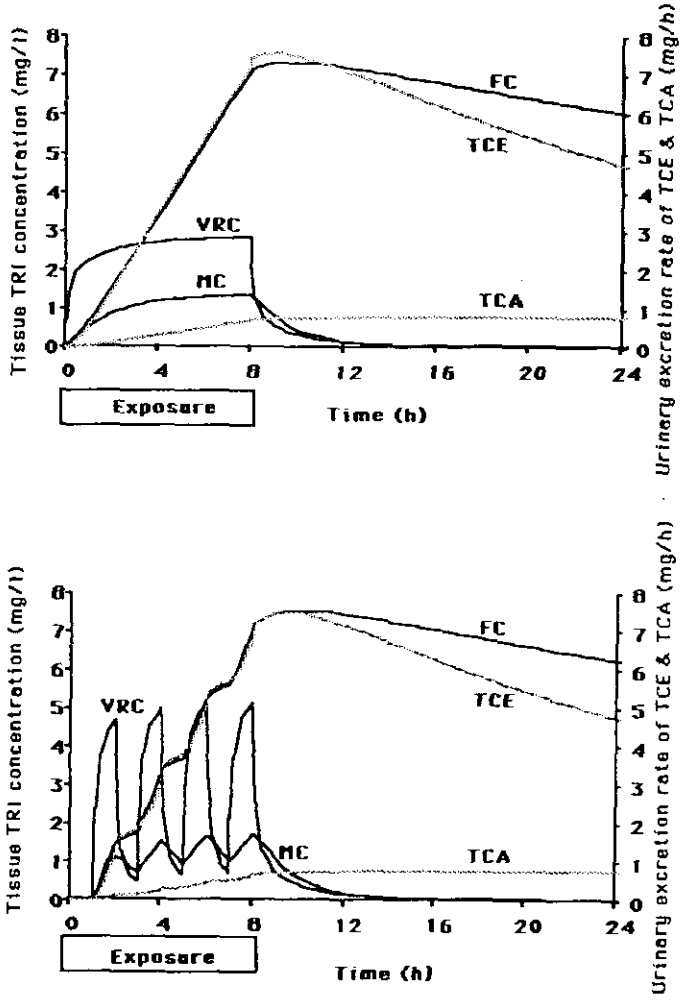
Slide 7: Continuous exposure



Slide 8: Intermittent exposure



Slide 9



Slide 10

INTERNAL DOSE IN CONTINUOUS AND INTERMITTENT EXPOSURE

Exposure	Internal dose	
	Trichloroethylene[a] (mg/l) x hr	Metabolites[b] mg
Continuous	7.71	332
Intermittent	7.53	336

[a]Area under the curve for blood concentration-time (120 hrs).

[b]Area under the curve for urinary excretion-time (120 hrs) = cumulative amounts of total trichloro-compounds.

Slide 11

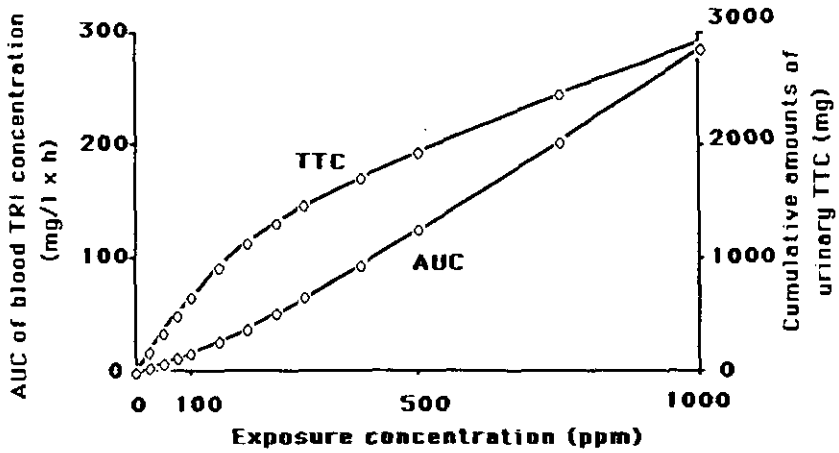


FIGURE 4. Dependency of internal doses of trichloroethylene (TRI) and its metabolites (TTC) on exposure concentrations of TRI. Simulation of 8-hour exposures. Internal dose of TRI was calculated as AUC of TRI concentration in blood; internal dose of TTC was calculated as AUC under the urinary excretion rate of metabolites.

Slide 12

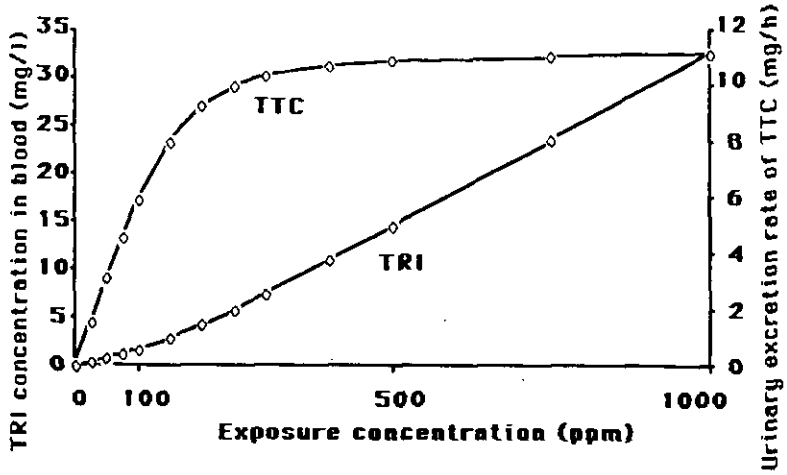


FIGURE 5. Dependency of trichloroethylene (TRI) concentration in blood and rate of urinary excretion of total trichloro-compounds (TTC) on exposure concentrations. Each value was obtained at the end of an 8-hour exposure.

Slide 13

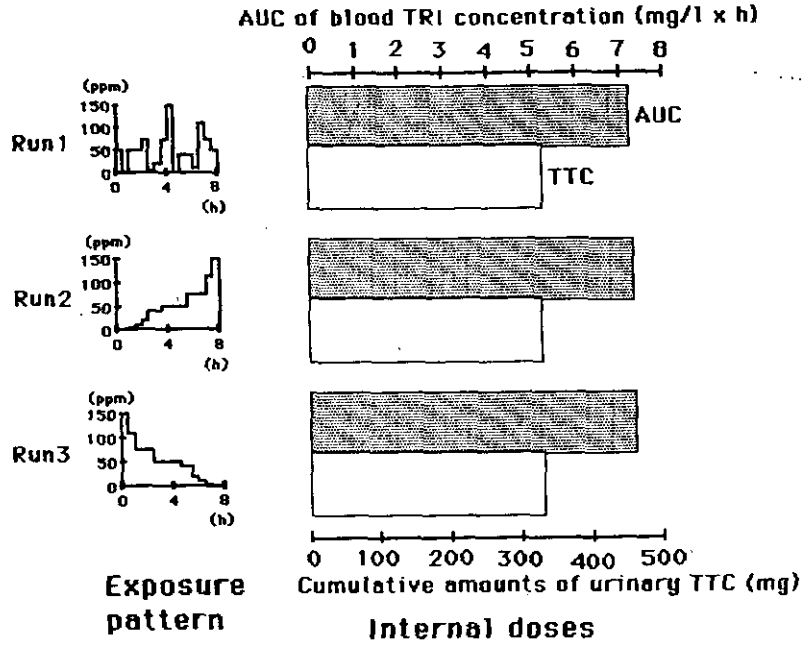


FIGURE 6. Dependency of internal doses of trichloroethylene (TRI) and its metabolites (TTC) on fluctuation of exposure concentration of TRI. Simulation of 8-hour exposures. Internal dose of TRI was calculated as AUC of TRI concentration in blood; internal dose of TTC was calculated as AUC under the urinary excretion rate of metabolites. Run 1, random; Run 2, incremental; Run 3, decremental type of exposure. The 8-hour TWA for all exposures equals 50 ppm.

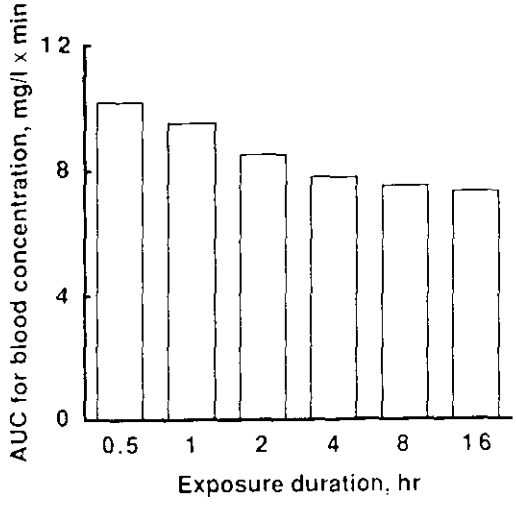
Slide 14

EXPOSURE CONCENTRATION AND DURATION EMPLOYED IN THE SIMULATION

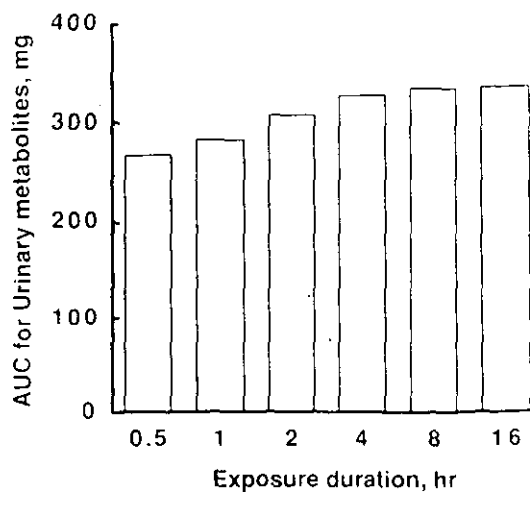
Duration, hr	Concentration, ppm
0.5	800
1.0	400
2.0	200
4.0	100
8.0	50
16.0	25

TWA concentration over 8 hours = 50 ppm or 400 ppm x hr.

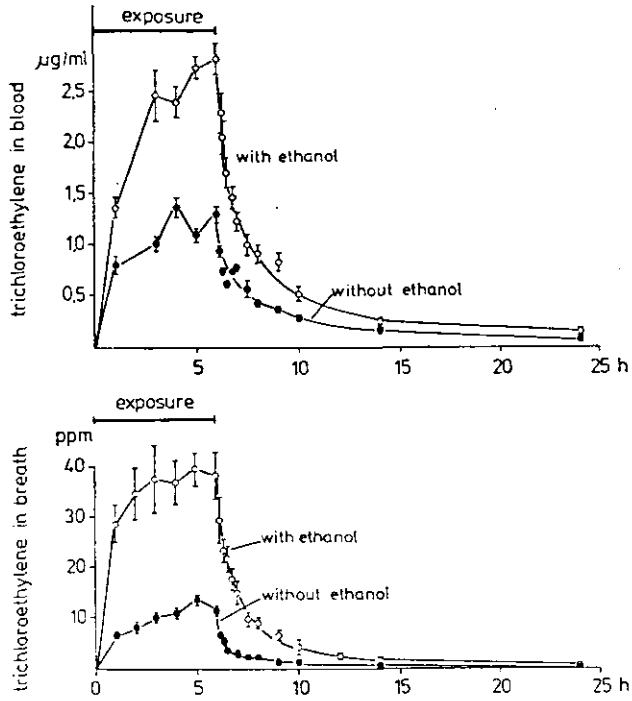
Slide 15



Slide 16

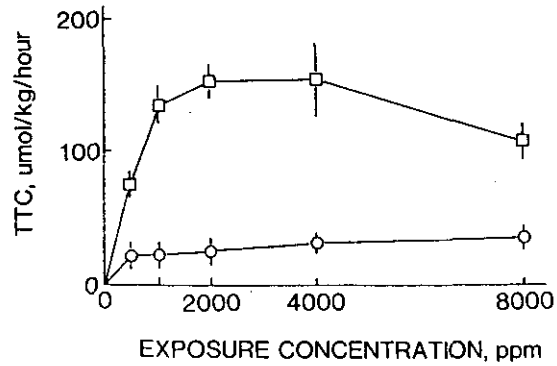


Slide 17



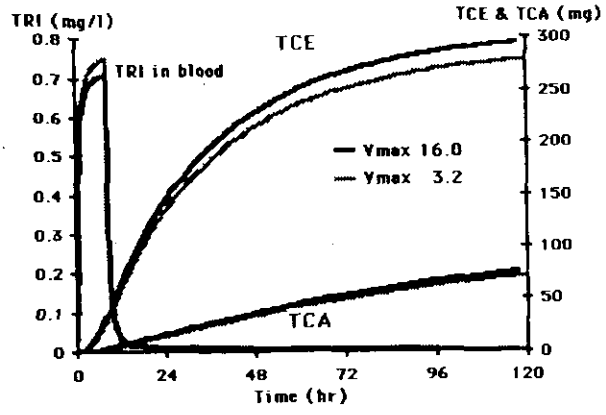
Trichloroethylene concentration in blood (top) and in breath (bottom) following inhalation of trichloroethylene by 6 volunteers (100 ppm, 6 hrs) both with and without ethanol (Miller et al, 1975).

Slide 18

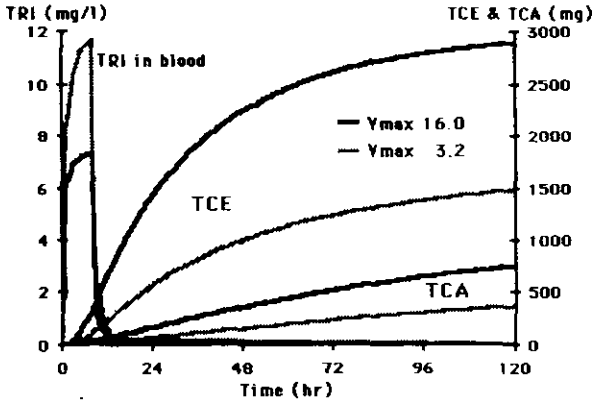


Ethanol-induced enhancement of trichloroethylene metabolism in rats.[22] KEY: □, ethanol-treated rats; ○, nontreated rats. A) Disappearance of trichloroethylene from the blood following a 2-hour inhalation exposure at 2000 ppm trichloroethylene. B) Urinary excretion rate of trichloroethylene metabolites (TCA + TCE) shortly after the end of a 2-hour inhalation exposure to trichloroethylene at various concentrations.

Slide 19

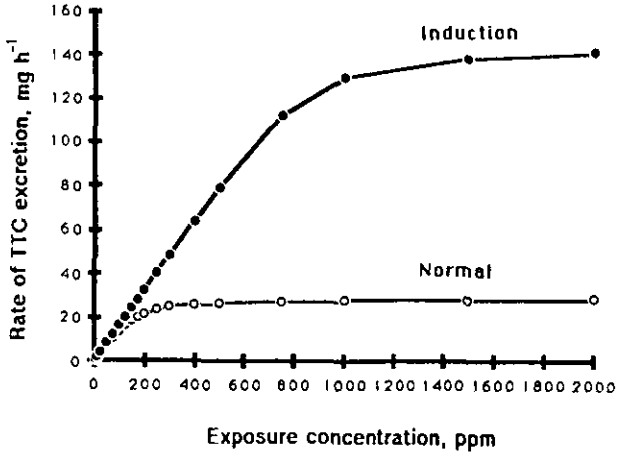


Slide 20



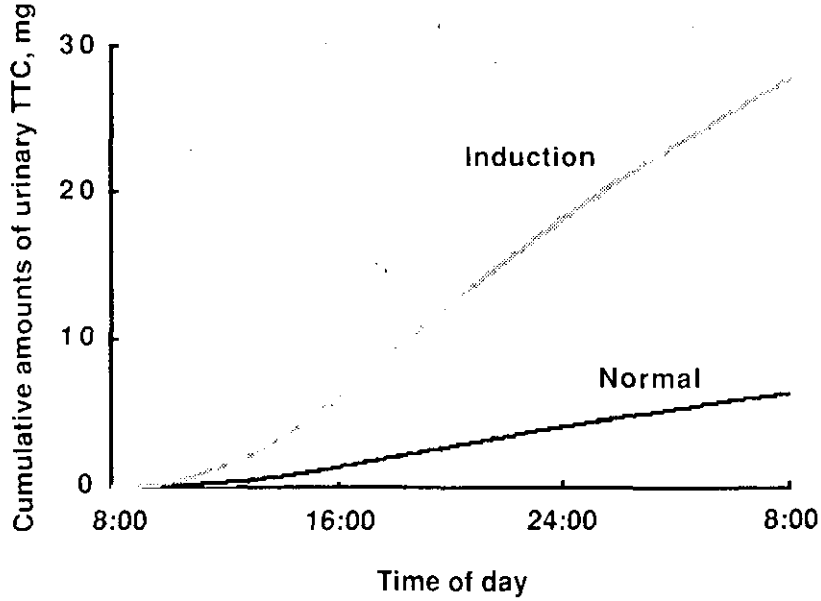
Effects of ethanol-induced enhancement of liver enzyme activity on pharmacokinetic behavior of trichloroethylene in man (simulation data). **Slide 19**: 8-hour exposure at 50 ppm of trichloroethylene. **Slide 20**: 8-hour exposure at 500 ppm of trichloroethylene.

Slide 21



Effects of enzyme induction on pharmacokinetics of trichloroethylene (TRI). The enzyme induction was assumed to increase Vmax of TRI metabolism 5-fold without changing Km. A standard male worker (70 kg) inhaled TRI at various concentration for 8 hours. Urinary excretion of TRI metabolites (total trichloro-compounds,TTC) is plotted against exposure concentration.

Slide 22



Effects of enzyme induction on pharmacokinetics of 1,1,1-trichloroethane. The enzyme induction was assumed to increase Vmax of 1,1,1-trichloroethane metabolism without changing Km. A standard male worker (70 Kg) inhaled 50 ppm of 1,1,1-trichloroethane for 8 hours. Time-course of urinary excretion of its metabolites (total trichloro-compounds, TTC) is shown.

Summary

Animal experiments often involve intense exposure which is unlikely to occur in humans. It is difficult to estimate the outcome of low concentration exposure by extrapolating the results of such high concentration exposure, because the metabolism of a chemical is often saturable at high concentration exposure. Linear extrapolation from high dose to low dose may lead to underestimation of the risk when the chemical itself produces toxicity and may lead to overestimation when the toxicity is mediated by activated metabolites. By using a physiological simulation model we can more appropriately extrapolate the dose-effect relationship obtained in small animals to humans.

TOXICOKINETICS OF DIOXIN AND RELATED COMPOUNDS

Jeremy J. Mills and Melvin E. Andersen

Chemical Industry Institute of Toxicology,
Research Triangle Park, NC, USA

INTRODUCTION

Dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD) is a potent carcinogen in both rats and mice (Kociba *et al.*, 1978, NIH, 1982). Its carcinogenicity is thought to be mediated by its action as a tumour promoter rather than as an initiator (Pitot *et al.*, 1980). At doses lower than those required for a carcinogenic response TCDD causes immunotoxic, teratogenic and reproductive effects (Buu-Hoi *et al.*, 1972, Courtney and Moore, 1971, Murray *et al.*, 1979). All of these toxic actions are believed to be mediated via the specific binding of TCDD to a cytosolic protein receptor, designated the *Ah* receptor. Following the formation of an *Ah* receptor-TCDD complex, and a cytosol-to-nucleus translocation, the complex binds with high specificity to DNA. This binding modifies the regulation of various genes, some involved in metabolic processes, and others with potential to alter cellular growth and differentiation (Gaido *et al.*, 1992). Due to this mechanism of action, TCDD has been referred to as a "receptor-mediated" carcinogen. Dioxin, in fact, is the most intensively investigated of a diverse family of chemicals, including other polyhalogenated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls, which can bind to the *Ah* receptor and affect cellular growth characteristics. The US EPA is currently reviewing its dioxin risk assessment with the stated intention of developing a generic approach to risk assessment for these "receptor-mediated" agents.

Among the hepatic proteins induced by the interactions between the *Ah* receptor-TCDD complex and DNA is a cytochrome, P-4501A2, which readily binds dioxin (Poland *et al.*, 1989) . The induction of this protein leads to a dose-dependent sequestration of dioxin in the liver. Any comprehensive model of TCDD pharmacokinetics must include a description of the induction of these binding proteins mediated by the interaction of the TCDD complex with DNA. Leung and coworkers developed a physiologically-based pharmacokinetic (PB-PK) model for dioxin in mice (Leung *et al.*, 1988) and rats (Leung *et al.*,1990). These models included protein induction in direct proportion to the level of occupancy of the available *Ah* receptor. In this paper we describe an extended PB-PK model that includes diffusion-limited distribution of TCDD and accounts for both physiological changes within the growing animal, and for induction of binding protein/enzymes by ternary interactions

between the TCDD-*Ah* receptor complex and DNA binding sites.

MODEL DEFINITION

The TCDD PB-PK model (Fig 1) consists of five distinct compartments: liver, fat, blood, slowly perfused and richly perfused tissues. The latter two compartments are representative of muscle/skin and kidney/visceral tissues, respectively. Each of the four tissue compartments has a specified tissue blood volume and a tissue compartment volume, taken from Bischoff and Brown (1966). The movement of the chemical into the tissue from the tissue blood compartment is proportional to a permeation coefficient-surface area cross-product (PA) for the tissue. Here tissue uptake is diffusion-limited when $PAt \leq Qt$. In the description of Leung and coworkers, tissue compartments had no specified blood volumes and were considered to be flow-limited. In addition there was strong binding in the blood which effectively decreased the rate of tissue uptake. Our enlarged model, because of the diffusion limited tissue compartments, does not require blood binding to match tissue uptake time course behavior. The relevant mass-balance equations are described below and abbreviations are defined in Appendix 1.

There are two mass-balance equations for each tissue; one for tissue blood (tb) and another for the tissue itself (t). Respectively,

$$dA_{tb}/dt = Qt\,(\,C_a - C_{vt}\,) + PA_t\,(\,C_t/P_t - C_{vt}\,) \qquad (1)$$

$$dA_t/dt = PA_t\,(\,C_{vt} - C_t/P_t\,) \qquad (2)$$

For the fat, slowly perfused, and richly perfused tissues, these equations are integrated for amount (A_{tb} or A_t), and concentrations are calculated by dividing the amount by the compartmental tissue volume. In the tissue, free (diffusible) concentration is calculated by dividing the tissue concentration (C_t) by the tissue partition coefficient (P_t), and C_{vt} represents the free concentration in venous blood leaving the tissue, as in equations (1) and (2).

In the liver the total mass is apportioned between free (partitioned) and bound forms of TCDD. C_{lf} is the free concentration in the tissue.

$$A_l = P_l\,V_l\,C_{lf} + BM1\,C_{lf}/(KB1 + C_{lf}) + BM2T\,C_{lf}/(KB2 + C_{lf}) \qquad (3)$$

The second term is the amount of the *Ah* receptor-TCDD complex (*Ah*-TCDD) and the third term represents the amount of the binding protein complex.

BM2T, the concentration of binding protein sites at time t, is calculated from the concentration of the *Ah*-TCDD complex, the DNA dissociation constant,

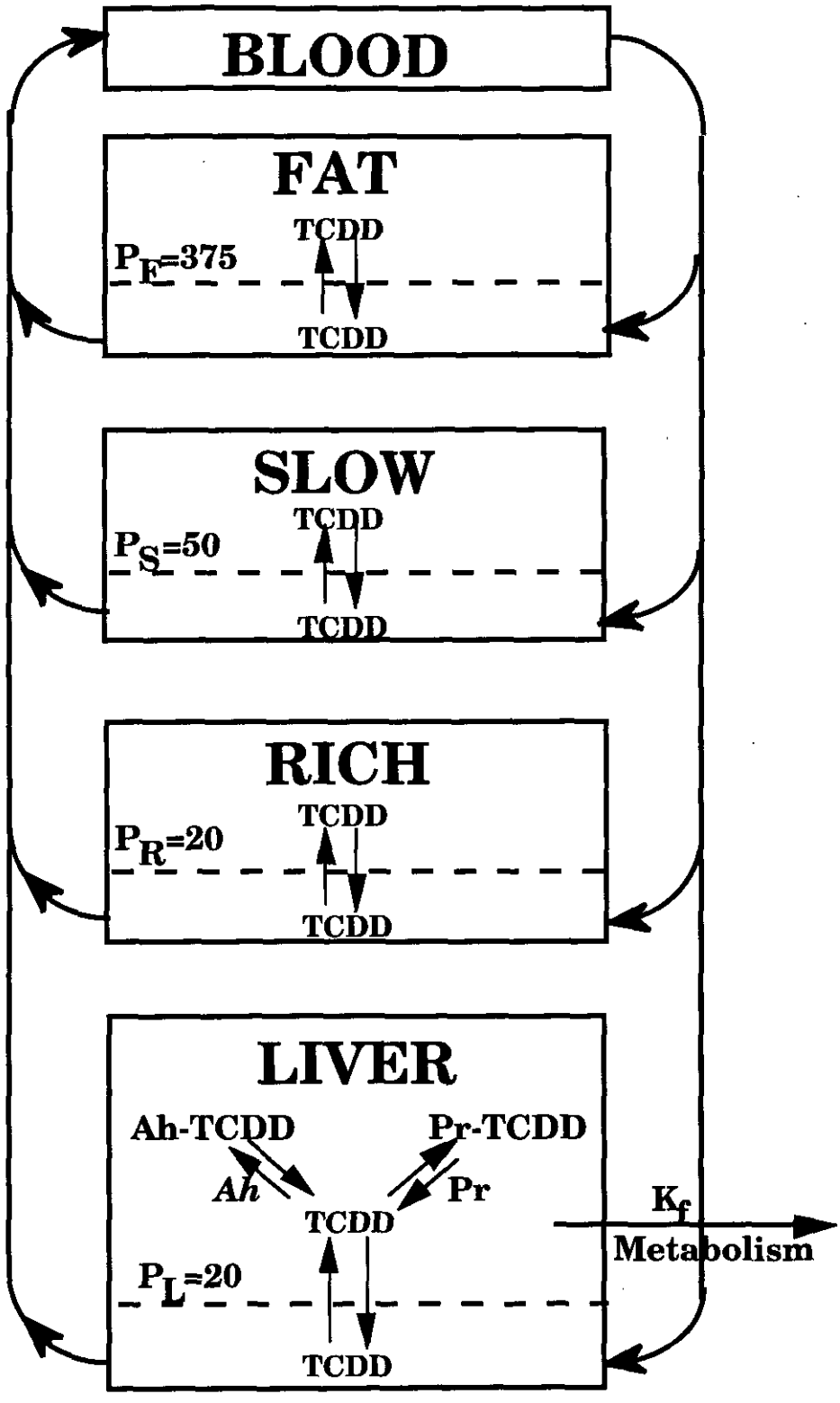


Fig 1. A schematic of the PB-PK model

and the basal and maximally induced concentrations.

$$BM2T = BM2O + BM2I\ (Ah\text{-TCDD})^n / ((Ah\text{-TCDD})^n + Kd^n) \quad (4)$$

Induction of cytochrome P-4501A1 activity, is modelled to occur with a half-life related to a 1A1 degradation rate constant (K_1). Eqn (5) below:

$$d1A1/dt = K0(1 + MAXIND(Ah\text{-TCDD})^{n1} / (Ah\text{-TCDD})^{n1} + Kd1^{n1}) - k_1 1A1 \quad (5)$$

RESULTS

The disposition of TCDD to the liver and fat is highly dose-dependent in the concentration range between 1 and 10,000 ng/kg bw (Fig 2). In this study (Abraham *et al.*, 1988) female Wistar rats received a single subcutaneous dose of TCDD and were killed seven days later. Concentrations are expressed as % dose/gm tissue and would be horizontal lines if disposition were dose-independent. The curvature is due to the induction of a high affinity binding protein, presumably cytochrome P-4501A2, by dioxin. The smooth curves were obtained with the PB-PK model based on the parameters in Appendix 1. For induction of the binding protein n was nearly 1 (1.05) with a small value for Kd (8×10^{-4}). The affinity of the induced protein for TCDD is 6.5 nM, using literature estimates of P-4501A2 concentration (Kedderis *et al.*, 1991). The value of n close to one indicates little interaction among TCDD-responsive DNA binding sites involved in expression of this particular gene.

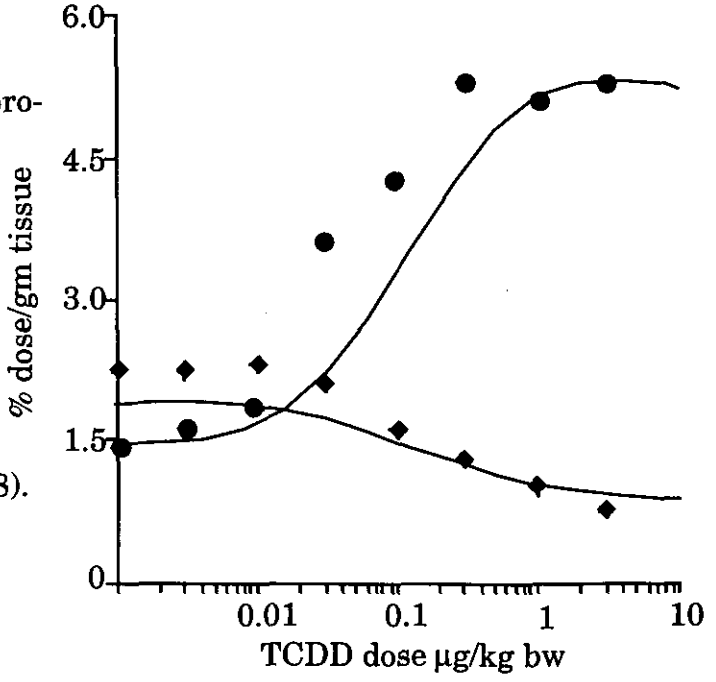


Fig 2. Dose-dependent disposition of 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin in female Wistar rats. Rats were administered [^{3}H]-TCDD s.c. in DMSO/toluene and sacrificed seven days later. Disposition of TCDD was assessed in Liver ● and Fat ◆ by liquid scintillation counting. Data are from Abraham and coworkers (1988). The smooth curves are model-generated simulations over the dose range shown.

The behavior of these curves at the lowest concentrations of TCDD is sensitive to *Ah* receptor binding parameters. The binding maximum, in the 2-4 pg/liver range, is lower than estimated *in vitro* by Scatchard plots, but is a consequence of the basal liver disposition. If BM1 were substantially greater the liver concentration at 1 ng/kg bw would be much higher than observed.

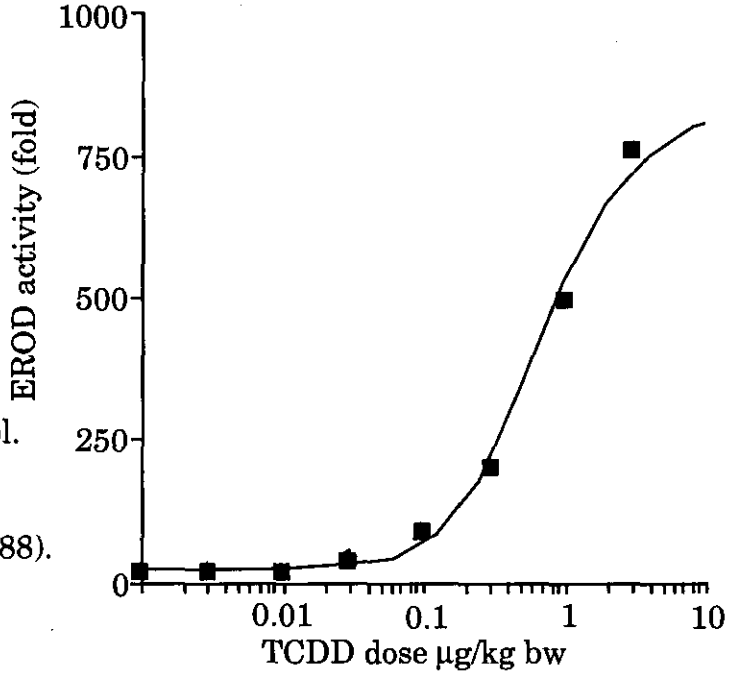


Fig 3. Dose response curve for cytochrome P-450 1A1-dependent ethoxyresorufin-*O*-deethylase activity. EROD activity was determined in liver microsomes isolated from rats administered TCDD and killed seven days later. Enzyme activity displayed as fold induction over control. The smooth lines are model simulations. Data are from Abraham and coworkers (1988).

The dose response curve for cytochrome P-4501A1 induction (Fig 3) was described with a similarly structured model, but required a higher value of n (2.3). This indicates a greater degree of positive interaction among the DNA binding sites for the *Ah* receptor-TCDD complex with this gene. The half maximal induction response for P-4501A1 occurs at about a 10-fold higher dose than the response of the binding protein.

The PB-PK model configured for these dose-response curves was also used to examine the time course of elimination after a single dose of 300 ng/kg bw (Fig 4). This experiment was especially useful for setting the metabolism rate constant for TCDD and the PA cross products (i.e., diffusion limitations) for the liver and fat. The simulation of these curves required the inclusion of time-dependent growth parameters over the 100 days of the experiment. Body weight changes were calculated from growth curves for female Wistar rats and the changes in organ size estimated relative to the body weight.

DISCUSSION

The half-life of TCDD in male rats was initially reported to be 20-30 days (Rose *et al.*,1976). However these early studies were carried out at high, inducing doses; elimination curves were obtained for only about 2 half-lives;

and analysis relied on chemical detection of TCDD in tissues. The half-life in hamsters was also estimated from time course data with a simple one-compartment model for dioxin kinetics, but used radiochemical detection of labelled TCDD. These various studies were relatively insensitive to the dose-dependent effects apparent when disposition is examined at much lower doses. Doses of 1 ng/kg bw cause minimal induction of the dioxin binding protein (Fig 2) or P-4501A1 (Fig 3). Protein induction does, however, become significant at 30-50 ng/kg bw and markedly alters dioxin disposition. Simple linear compartmental models completely ignore these complexities. Over the past five years we have been developing physiologically-based pharmacokinetic models of TCDD to examine the biological determinants of disposition in a quantitative manner.

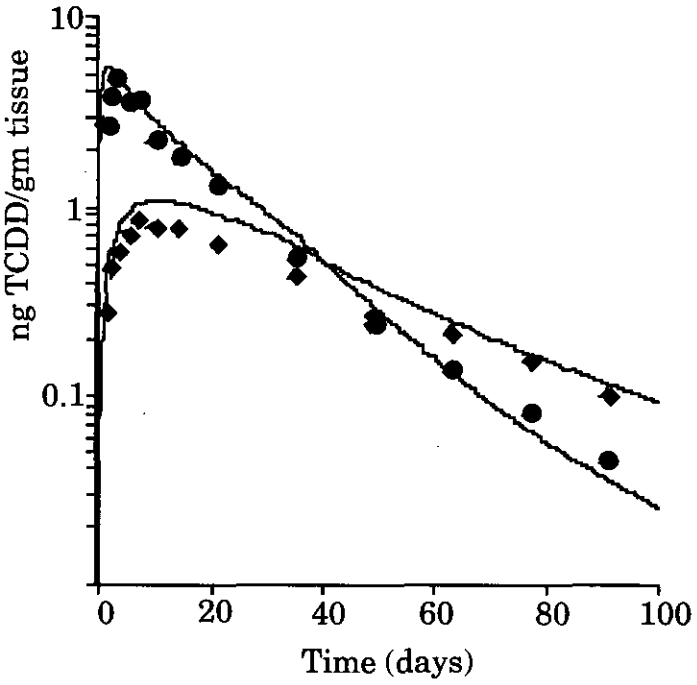


Fig 4. Time-dependent tissue disposition in female Wistar rats following a single s.c. dose of [^{3}H]TCDD at 300 ng/kg bw. At each time point tissues were removed and TCDD levels determined by liquid scintillation counting. Liver ● and Fat ◆ are displayed with smooth curves generated by the PB-PK model. Data are from Abraham and coworkers (1988).

Our PB-PK model, as presently configured, has diffusion limited TCDD uptake, partitioning in all tissues, except the liver, related to lipophilicity, specific binding to two protein species in the liver, and hepatic metabolism as the only route of elimination from the organism. Tissue blood flows were set consistent with values used in other PB-PK models. Growth rates were incorporated to account for the disproportionate increase in fat, a major tissue depot for TCDD. With the blood flows and tissue volumes set, analysis of time course curves (Fig 4) provided estimates of the tissue diffusion clearances and partition coefficients. Diffusion clearance in fat is 1/10th of fat blood flow.

The challenge in providing a biologically realistic kinetic model for dioxin is the need not only to account for the determinants of disposition (i.e., tissue partitioning, biotransformation rates, and protein binding constants), but also to describe the pharmacodynamic events related to the self induction of TCDD binding protein species in the liver. Knowledge of the molecular

mechanisms of the interactions of of the *Ah* receptor-TCDD complex with regulatory regions of specific genes is growing rapidly, but already clearly shows the role of ternary *Ah* receptor-TCDD-DNA complexes in regulating gene transcription. Our present model of disposition is based on a ternary complex being obligatory for the pharmacodynamic action of TCDD at the genomic level. In describing these interactions we require estimates of binding constants between the *Ah* receptor and TCDD and between the *Ah* receptor-TCDD complex and sites on DNA. These ternary interactions with DNA then enhance transcriptional processes leading to increased amounts of specific dioxin-binding proteins, presumably cytochrome P-4501A2.

The concentration of cytochrome P-4501A2 is increased about 10-fold on complete induction with dioxin congeners. Our values for basal 1A2 (10 nmoles/liver) and maximally induced levels (110 nmoles/liver) are consistent with direct determinations of this protein. The binding constant, KB2, was estimated by curve fitting with Figure 2.

The binding properties of the *Ah* receptor are largely estimated from the tissue concentration of TCDD at non-inducing levels (especially sensitive to BM1, the *Ah* binding maximum) and the placement of induction along the dose axis (sensitive to KB1, the Ah binding affinity). The other important constant, Kd, for the DNA interactions with the *Ah* receptor-TCDD complex also affects the placement of the induction curve, whether for 1A1 or 1A2, along the dose axis. The Hill-type coefficients (n and n1) control the steepness of the induction response. Of the two responses examined induction of 1A2 (liver sequestration) shows a higher affinity but lower cooperativity than 1A1 induction. This observation of cooperativity in 1A1 induction is consistent with the observation that there are at least 4 dioxin-responsive elements (DREs) in the regulatory region of this gene (Whitlock, 1990).

Our model structure presently has a single type of *Ah* receptor -TCDD complex that interacts with DNA binding sites of variable affinity. More complex models with different *Ah* receptor-TCDD complexes (due to other protein interactions, for instance) might lead to different conclusions about cooperativity, but these models do not seem warranted by available data at this time.

The basic behavior of dose-dependent hepatic sequestration is a characteristic of many congeners of dioxin (Safe, 1990) and is observed in multiple species including people (Carrier and Brodeur, 1991). Thus this basic model structure appears to be widely applicable with these various chemicals that act *via* the *Ah* receptor.

In conclusion, a generic PB-PK model has been developed to describe the disposition and enzyme-inducing properties of TCDD. Ternary interactions

between the *Ah* receptor, TCDD and DNA binding sites lead to enhanced production of various proteins, including specific hepatic proteins that bind TCDD. Induction of these proteins leads to dose-dependent liver accumulation of TCDD. With appropriate values for partition coefficients, binding constants and metabolic rates this model will also prove to be useful for describing the kinetics and dynamics of many xenobiotics that interact via the *Ah* receptor and affect gene expression.

REFERENCES

Abraham K., Krowke R., and Neubert D. (1988) *Arch. Toxicol.* **62**: 359

Bischoff K., and Brown R. (1966) *Chem. Eng. Prog. Symp. Ser.* **62**: 33

Buu-Hoi N., Chanh P., Sesque G., Azum-Gelade M., and Saint-Ruf G. (1972) *Naturwissenschaften* **59**: 174

Carrier G., and Brodeur J. (1991) *Toxicologist* **11**: 895

Courtney K., and Moore J., (1971) *Toxicol. Appl. Pharmacol.* **20**: 396

Gaido K., Maness S., Leonard L., Greenlee W. (1992) *J. Biol. Chem.* in press

Kedderis L., Diliberto J., Linko P., Goldstein J., and Birnbaum L. (1991) *Toxicol. Appl. Pharmacol.* **111**: 163

Kociba R., Keyes D., Beyer J., Carreon R., Wade C., Dittenber D., Kalnins R., Frauson L., Park C., Barnard S., Hummel R., and Humiston C. (1978) *Toxicol. Appl. Pharmacol.* **46**: 279

Leung H., Ku R., Paustenbach D., and Andersen M. (1988) *Tox. Lett.* **42**: 15

Leung H., Paustenbach D., Murray F., and Andersen M. (1990) *Toxicol. Appl. Pharmacol.* **103**: 399

Murray F., Smith F., Nitschke K., Humiston C., Kociba R., and Schwetz B. (1979) *Toxicol. Appl. Pharmacol.***50**: 241

NIH (1982) *NTP Report Series* No. **209**

Pitot H., Goldsworthy T., Campbell H., and Poland A. (1980) *Cancer Res.* **40**: 3616

Poland A., Teitelbaum P., Glover E., and Kende A. (1989) *Mol.Pharmacol.* **36**: 121

Rose J., Ramsey J., Wentzler T., Hummel R., and Gehring P. (1976) *Toxicol. Appl. Pharmacol.* **36**: 209

Safe S. (1990) *Crit. Rev. Toxicol.* **21**: Issue 1

Whitlock J. Jr., (1990) *Ann. Rev. Pharmacol. Toxicol.* **30**: 251

This work was co-sponsored at CIIT by a grant from the American Paper Institute

APPENDIX 1

Parameters and values for the physiological dosimetry model for TCDD

Model parameter	Abbreviation	Wistar Rat
Partition Coefficients		
Liver/blood	Pl	20
Fat/blood	Pf	375
Richly perfused/blood	Pr	20
Slowly perfused/blood	Ps	30-50
Metabolic Constants *		
First order rate constant	Kfc	1.75
Induction (fold over basal)		2.00
Protein Binding		
Ah maximum (pmoles/liver)	BM1	3.75
Ah affinity (pM)	KB1	35
1A2 basal level (nmoles/liver)	BM2O	10
1A2 maximum (nmoles/liver)	BM2I	110
1A2 affinity (nM)	KB2	6.5
Induction Characteristics		
1A2 - Hill term	n	1.05
1A2 - Hill binding constant	Kd	$8x10^{-4}$
1A1 - Hill term	n1	2.25
1A1 - Hill binding constant	Kd1	$1.89x10^{-3}$
1A1 basal synthesis rate (U/hr)	K0	0.7
1A1 degradation rate	k1	0.035
1A1 maximum fold induction	MAXIND	50

* The metabolic rate constant is assumed to be induced a maximum of 2-fold.

Health risk assessment of toxic metals

Monica Nordberg, Ph.D.
Department of Environmental Hygiene
Karolinska Institutet
S-104 01 Stockholm, Sweden

Mr Chairman, ladies and gentlemen. I am grateful to the organizers having invited me to this workshop and thus, made it possible for me to visit Japan and to participate in this workshop.

Introduction

In my presentation on health risk assessment of toxic metals I aim to focus on some particular metals, e.g. lead, cadmium and mercury. These metals will be presented individually and in the different chemical forms.

Human beings are exposed to several metals. Many metals are regarded as essential and important for life. However, under certain circumstances they might become toxic and cause adverse health effects. This happens when, for example, exposure is excessive, exposure route is not the physiological one or the chemical form - the species - is not acceptable to the human being. An increasing mobility of metals caused by acidification of soil and lakes increases human exposure via the food chain and/or drinking water. Many metals are known to be toxic to humans - Documentation from work environment has shown this e.g. for lead, mercury and cadmium. Today these metals have been shown in certain parts of the world to cause adverse health effects even in the general population. Under what circumstances are we exposed to the metals? Is it by air or by food intake?

The exposure route reflects the presence in our environment. It could for the metals, I am going to give a more general overview, very well be that one is exposed in the work environment by inhalation and in the general environment - at home - so to say by presence in food stuff. An increased interest how the metals exist in the ecological system is obviously due to increased acidification in nature. Many metals and their compounds get an increased mobility with lower pH thus, we get an increased exposure. However, for selenium it is the opposite, the lower pH the less mobile selenium is present. Selenium is known to serve as free radical scavenger and to increase activity for the enzyme glutathione peroxidase (GSH-px). Selenium and GSH-px are involved in mechanisms protecting development of cancer. To discuss unwanted effects - adverse health effects - one has to define whether the metal or the metal speciated causes cancer, local or systemic toxic effects. To improve science and thus, giving us more uunderstanding why and when we get ill after exposure, studies on the mechanisms are highly valuable. To gain total knowledge means it could be possible to protect humans to develop adverse health effects. Each metal has its own panorama of effects and because of this each metal has to be dealt with separately. The mechanisms behind metal toxicity are most by interference with biochemical systems in the cell.

For health risk assessment identification, with regard to speciation of metal compound, has to be performed. To have metabolic model for the compound is of great advantage. This is, however, only possible if complete knowledge of metabolism and kinetics including biological half-time, critical organ, excretion, interaction is available. If not, one has to start with summarizing present knowledge.

Results from animal experiment and results from epidemiological studies contribute to increased knowledge of the substance. Results from short-term testing could as well be included. Different dose levels give different effects.

Risk assessment is performed stepwise. People involved in risk assessment are mostly trained physicians, toxicologists or chemists. First of all the risk has to be identified with regard to what agent causes the effect. Knowledge where agent and risk is found has to be summarized. Identifying risk could be through case reports which is the case e.g. for cadmium.

Risk estimation and evaluation is the next step and already mentioned categories could deal with this step.

Administrative regulation is finally what the community has to deal with. Giving guidelines and regulatory values is a question for each country. After listening to scientists about risks for developing adverse health effects, socio-economic factors are considered when setting limits for regulating environment in order to protect humans. Collaboration and exchange of knowledge from all over the world facilitate this process.

Metal toxicity

Toxic effects caused by metals can be biochemical changes in critical organ or cancer. For metals causing health effects to human beings other than cancer increased exposure means increased severe effects and increased number of affected. Studying dose and effect relationship is highly recommended. Due to a variation in sensitivity for develop-

ing toxic effects among human beings dose-response relationships is as well necessary to establish. Dose-relationship is defined as percentage of population with a specific effect related to dose. To establish dose-effect and dose-response relationship for each metal is fundamental for risk estimation. To gain information on concentration of metals it is important to consider the value of techniques for metal analyses and analyses for detecting effects. Questions to be raised are such as: Are the values obtained correct? This is of particular interest when the concentration is low. Quality control including reference samples of the techniques used is understood as most important for underlining the correctness of obtained results. An important part of the analyses is how sampling is performed. Sampling tubes and equipment should not contribute with metals to the sample and not bind the metals to surface in the sampling equipment.

Biological monitoring of metals is considered important to the extent that the Scientific Committee on the Toxicology of Metals under the Permanent Commission of Occupational Health organized a meeting in 1986.

Risk identification and risk assessment are of importance and is practised in biological monitoring. This includes as well evaluation and quality control of obtained data and used methods for analyses.

A presentation of lead, cadmium and mercury will be presented in figures and tables.

Cadmium is chosen as example showing how risk assessment can be performed from especially the biochemical point of view.

References

Nordberg GF., ed (1976) Effects and Dose Response Relationships of Toxic Metals. Proc. Int. Meeting, Tokyo, Nov. 1974. Elsevier Publ., Amsterdam.

Friberg L, Nordberg GF, Vouk VB., eds. (1986) Handbook on the Toxicology of Metals. Vol I and II. Elsevier, Amsterdam.

Clarkson TW, Friberg L, Nordberg GF, Sager PR., eds. (1988) Biological Monitoring of Toxic Metals. Plenum Publ. Co.

Nordberg M. (1978) Studies on metallothionein and cadmium. Environ. Res. 15:381-404.

Nordberg M. (1984) General aspects of cadmium. Transport, uptake and metabolism by the kidney. Environ. Health Perspect. 54:13-20.

ENVIRONMENTAL EPIDEMIOLOGY OF MINAMATA DISEASE
with special emphasis on its relevance to risk assessment of methylmercury

Hiroo Kato, M.D.
National Institute for Minamata Disease

An unclarified disease of the central nervous system occurred in around 1955 among fishermen and their families in the Minamata bay area. Epidemiological, clinical and pathological studies demonstrated that it was due to methylmercury poisoning by large intake of polluted fish. Methylmercury, produced as a by-product from mercuric sulfate which was employed as a catalyst in the production of acetaldehyde from 1950's to 1960's at a chemical plant located in Minamata City, had been released into the sea together with waste water, and it had accumulated in fish as a result of the biological concentration process.

About 2,000 patients with typical symptoms have been designated for compensation, but there possibly may be twice as many additional persons who suffer from health disturbances such as sensory disturbances of the limbs. This tragic event has been frequently referred to as the original incident from industrial pollution.

In 1965, about 10 years later, another methylmercury poisoning occurred among residents along the Agano River in Niigata Prefecture due to the large intake of contaminated freshwater fish. These patients had been similarly caused by methylmercury, which had been released into the river from an upstream chemical plant where methylmercury was produced as a by-product in the

production of acetaldehyde.

Extensive studies of patients in the Minamata and Agano River areas together with experimental research lead to the determination of the etiology and mechanism of toxicity as well as the establishment of methods for the objective diagnosis and therapy of this disease. For the purpose of risk assessment, however, it is unfortunate that no basic data are available for the determination of dose-response relationships in the exposed population, except for the clinical report which attempted the estimation of the minimum required concentration of methylmercury for onset of disease from examination of hair from Minamata Disease patients in Niigata.

When patients were first seen in the Minamata bay area, initial efforts had been focused on the determination of the cause. Several years later, methylmercury was suspected to be the etiology, and measurements of the methylmercury content of hair were first made in 1960 to 1962 at time of health examinations of residents of the polluted area. Because the temporal trend of mercury concentration is unknown, it is not possible to derive an estimate of the maximum concentration from these measurements for each individual, and thus a precise estimate of the dose-response can not be made.

The experience in Minamata was available for studies in Niigata, and a program of health examinations of residents of the polluted area was begun soon (four months) after the recognition

of the first patient, including the collection of hair for methylmercury content determinations. A retrospective cohort study was recently conducted by Dr. Kinjo and other epidemiologists of this Institute in collaboration with Professor Takizawa of Akita University in which analyses of the dose-response and estimation of the threshold were made using the hockey-stick model based on the incidence of Minamata Disease among those with earlier hair mercury content determinations.

This report will present the preliminary results of this study, in which the roster of 1200 residents who had hair methylmercury content measurements in 1966 was matched against an updated roster of designated patients with Minamata Disease. The maximum concentration for each patient was estimated from the hair measurements using a single compartment model and using data on the temporal change in hair mercury concentration from measurements of a small segment of the long hair of some of the patients. The length of the collected hair, the hypothesized length of the biological half-time, etc. which act as uncertainty factors in the estimate were examined for the magnitude of their effects upon the estimation of the threshold dose. The effects of possible modifiers such as age at exposure and sex were also examined.

An on-going long-term mortality follow-up of Minamata Disease patients is being conducted to determine whether there are any possible late effects or complications. The most recent results show excess mortality from diseases of the liver and kidney, but no excess mortality from cancer has been found thus

far. A morbidity follow-up is also being conducted in conjunction with annual health examinations provided to the elderly population under the provisions of law in a small town near Minamata City to determine whether there is any accelerated aging among Minamata Disease patients.

Children, who had been exposed in utero to methylmercury due to the intake of contaminated fish by their mothers, unlike adult exposed patients, have mental retardation. Statistical analysis of the dose response in 84 mother-child pairs in the Iraq incident suggests that the threshold dose for motor retardation (walking, speech) may be as low as 10 to 20 ppm methylmercury in the hair of the mother. This estimate for in-utero exposure is very low in comparison with that for adult exposure, i.e. 50 to 125 ppm in the 1990 IPCS publication on methylmercury. Uncertainties in the Iraq data, which are largely due to the very small number of cases, are not negligible, and therefore IPCS has recommended the conduct of well designed epidemiological studies in populations having a high consumption of fish. Experiments are being conducted at this Institute using newborn rats (corresponding to the later period of pregnancy in humans) in an effort to determine the threshold dose (minimum effect) of methyl mercury based on behavioral tests.

In Japan, it is customary to preserve the navel cord to commemorate childbirth especially in rural area. At time of the Minamata incident, the temporal change in methylmercury content was estimated by measurements of the preserved navel cord of

children born at about the time the pollution had occurred. Unfortunately, no follow-up of these children was made. plans are being considered for an extensive retrospective study to examine the methylmercury content measurements of the navel cord in relation to subsequent growth and developmental data for the retrospective determination of the possible dose-response relationship.

In incidents involving chemical environmental pollution, it is generally rare that risk assessment can be made based on the dose-response in the exposed population. Minamata Disease is not an exception. More progress in general has been made in risk assessment associated with exposure to environmental radiation in comparison with environmental pollution by chemical substances. The method of risk assessment for atomic bomb radiation, which is a typical example, will be described and compared as much as possible with the experience with Minamata Disease in terms of such factors as research design, estimate of individual dose, type of dose-response, etc., which affect the estimation of the life-time risk.

IN VITRO TOXICITY TESTING AND RISK ASSESSMENT[1]

John M. Frazier, Ph.D.
Division of Toxicological Sciences
The Johns Hopkins University
615 N. Wolfe Street
Baltimore, Maryland 21205, U.S.A.

A major objective of the toxicological sciences is to predict the *in vivo* toxicological consequences of human exposure to pure chemicals, complex mixtures and commercial formulations. Historically, the experimental approach to this goal has been to investigate toxicological processes in whole animal models and extrapolate the results obtained (using various extrapolation processes, such as high dose - low dose extrapolation, interspecies extrapolation and route-to-route extrapolation) to predict human toxicity. *In vitro* model systems have played an increasingly important role in this process, and the toxicological parallelogram (Figure 1), which relates *in vitro* responses between species to assist in the *in vivo* species extrapolation, has gained wide spread acceptance in the safety evaluation process. Traditionally, *in vitro* toxicological models have played a major role in

[1] Portions of this abstract have previously appeared in Frazier, J.M. 1991. General perspective on in vitro toxicity testing. In Frazier, J.M. (Ed.) In Vitro Toxicity Testing: Application to Risk Assessment. Marcel Dekkar, New York, 1991. pp. 1-11.

understanding mechanisms of action of toxicants at the molecular and cellular level. Thus, *in vitro* models are an established component of toxicological risk assessment.

Technological developments in both cell culture and bioanlytical methodology have significantly improved the capabilities of *in vitro* models to provide relevant and reliable toxicological data. In order to fully utilize information provided by *in vitro* toxicological models, it is essential to develop new theoretical and experimental methodologies to extrapolate *in vitro* toxicity data to predict *in vivo* toxicity responses (*in vitro - in vivo* extrapolation).

The theoretical basis for predicting *in vivo* toxicity lies in an understanding of the toxicological process (Figure 2) and quantification of this process in terms of the dose-response relationship. The conceptual connection between exposure and a toxicological effect can be segregated into three components: toxicokinetics, initiation and toxicodynamics. There is an underlying casual connection between these components, e.g. initiation of toxicity by the molecular interaction of the toxicant with a molecular target cannot occur prior to the arrival of the toxicant or its metabolite at the site of action. Similarly, pathological responses at the organ level do not develop prior to responses at lower level of biological organizations. Thus, the probability that a given exposure (E) will result in an observed

toxicological effect (TE) at some level of biological organizations [P(TE,E)] can be described as the product of three terms:

$$P(TE,E) = P_K(X,E) * P_I(CE,X) * P_D(TE,CE)$$

where $P_K(X,E)$ is the probability that given a particular exposure a concentration X of the active form of the toxicant will occur at a specific tissue, $P_I(CE,X)$ is the probability that given a particular concentration of the active toxicant, X, there will be a cellular effect (CE), and $P_D(TE,CE)$ is the probability that given a particular cellular effect, ultimately there will be expressed a measurable toxic effect at a higher level of biological organization. Any one of these three factors, or a combination, can be instrumental in determining target organ toxicity *in vivo*.

In order to improve our ability to predict *in vivo* target organ toxicity, new methods are needed to quantitatively evaluate these probability factors. Currently, *in vitro* toxicological models are being used widely to estimate $P_I(CE,X)$, since this probability represents the molecular/cellular response to the chemical under investigation.

IN VITRO TOXICITY TESTING

The various roles that *in vitro* toxicity testing can play in toxicological evaluations relate to the fundamental concept that

toxicological effects are a consequence of the interaction of the toxicant and/or a reactive metabolite with a molecular target on or within a sensitive cell type. Thus, the response of cellular systems in culture to test chemicals can be related to the central events in the toxicological process (Fig 2). For this reason, *in vitro* toxicity testing systems can be effectively utilized in various aspects of safety/hazard evaluations, including but not limited to: (1) ranking chemicals for their intrinsic potency, (2) identifying mechanisms of toxic action, and (3) identifying potential target organ toxicity.

The ranking of chemicals for their toxicity to cells *in vitro* provides useful toxicological information. It is clear from the toxicological process described in Figure 2 that many factors in addition to the specific cellular response to chemicals determine the overall dose-response relationships *in vivo*. However, the central component of the process is the interaction of the toxicant and/or its metabolites with molecular targets at the cellular level. Thus, an evaluation of the relative potency of a new chemical in cellular systems, in comparison with known benchmark chemicals, will provide an indication of the potential hazard of a new chemical at a fundamental level. There are limitations to the interpretation of this data in the context of *in vivo* toxicological responses. These limitations are mainly due to the complex modulation of the *in vitro* response by kinetic, interactive and repair processes *in vivo*. However, a new chemical which elicits

severe toxic responses in cells at extremely low concentrations (submicromolar concentrations) will in all likelihood have limited commercial applications due to *in vivo* toxicity.

The concept of potency based on a single *in vitro* measurement can be expanded to include a spectrum of endpoint measurements which together can be used in a diagnostic sense to elucidate the mechanisms of action of a toxicant. Mechanistic studies using *in vitro* systems are not new and have been a component of the safety/hazard evaluation process for many years. However, in the past these studies were usually conducted late in the development process, often to resolve mechanistic questions which arose in animal studies. The concept proposed here is to utilize multiple endpoint measurements in a decision tree design to rapidly evaluate the intrinsic cellular toxicity of a chemical as an early step in the toxicological evaluation process. Having this information initially will allow for better design of animal studies which may follow or, better yet, the information developed may be adequate to undertake the toxicological decision without resorting to *in vitro* studies.

A third use for *in vitro* toxicity testing systems is in the area of target organ toxicity identification. By using a spectrum of cell types representative of various potential target organs (hepatocytes, proximal tubular cells, neurons, cardiac myocytes, etc.) it would be possible to determine if any particular cell type

is significantly more sensitive to an unknown toxicant. If metabolic activation is a question of concern, the representative cell types could be cultured in the presence and absence of a metabolizing system, either a cell-free extract (S9) or cocultured with isolated hepatocytes. Identification of sensitive cell types could improve *in vivo* toxicity testing by suggesting specific clinical measurements which should be included in the *in vivo* experimental design to improve chances of detecting adverse effects.

These three examples - potency testing, mechanisms identification, and target organ identification - are indicative of the role in vitro toxicity testing systems can play in the safety/hazard evaluation process.

RISK ASSESSMENT

The major limitation to the replacement of *in vivo* animal testing with *in vitro* toxicity testing approaches is the issue of *in vitro-in vivo* extrapolation. The critical question is how to utilize the *in vitro* toxicity testing database to make intelligent predictions of *in vivo* toxicity. This problem has not been thoroughly explored and the extrapolation techniques must be developed; a successful resolution of this problem will require a significant research effort. *In vitro* toxicity testing provides a concentration-response relationship for some relevant marker of

toxicity in some particular cell types. The goal is to predict what the dose-response relationships will be *in vivo*. Assuming human cells are employed in the testing system so that species extrapolations are not a concern, then two components must be incorporated into the *in vitro - in vivo* extrapolation: the toxicokinetics component, which would predict the exposure dose of the chemical that results in extracellular concentrations at the target tissue equivalent to the concentrations *in vitro*, and the toxicodynamic component, which would modulate the *in vitro* cellular response by various factors, such as tissue repair processes or induction of inflammatory reactions. Experimental and theoretical techniques to predict the appropriate correction factors must be investigated and incorporated into an *in vitro - in vivo* extrapolation algorithm.

Finally, when both testing and extrapolation techniques have been established, it may be possible to conduct a significant portion of the safety/hazard evaluations on the basis of these newer technologies. A possible scheme for toxicological evaluations in the future would include *in vitro* toxicity testing, structure-activity methodologies (which would draw heavily on historical databases), physiologically based toxicokinetic modeling and *in vitro* toxicokinetic studies, and finally the *in vitro-in vivo* extrapolation process to integrate the data provided by the various techniques to make predictions of *in vivo* toxicity (Figure 3). Focused research will be needed to implement fully this global

approach; however, in the meantime piecewise implementation of various components of the process will continue to improve the safety/hazard evaluation process.

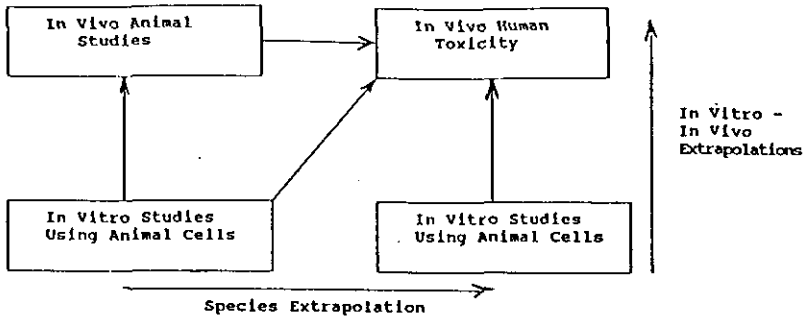


FIG. 1. The toxicological parallelogram. *In vitro* toxicological studies in animal cells are compared to *in vivo* toxicity in animals to obtain a scalling factor to apply to *in vitro* studies in human cells in order to predict *in vivo* human toxicity. Many investigators are exploring the possibility of using *in vitro* studies in animal cells to directly predict *in vivo* human toxicity.

The Toxicological Process

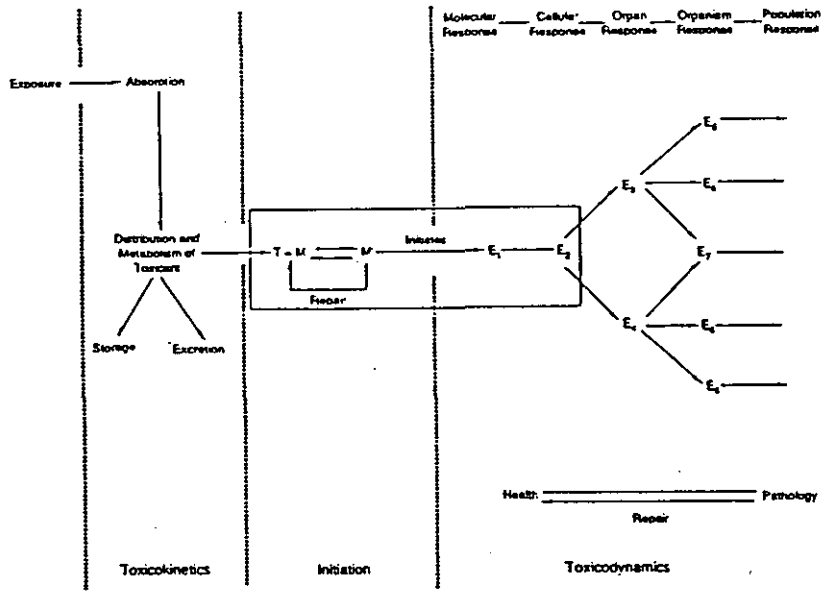


FIG. 2. The toxicological process. Expression of toxicity in any biological system is the culmination of many interacting processes including toxicokinetics, initiation and toxicodynamics. Toxicological processes control the delivery of the active form of the toxicant T to the site of interaction with molecular targets, M. The molecular interaction between the active form of the toxicant and the molecular target results in alterations in cellular macromolecules, M*, which initiates the cascade of biological events referred to as toxicodynamics. These events begin at the molecular and cellular levels and ultimately propagate to higher levels of biological organization. *In vitro* toxicity testing systems can evaluate the toxicological events at the molecular and cellular levels (indicated by the central box in the Figure) which are at the core of the toxicological process.

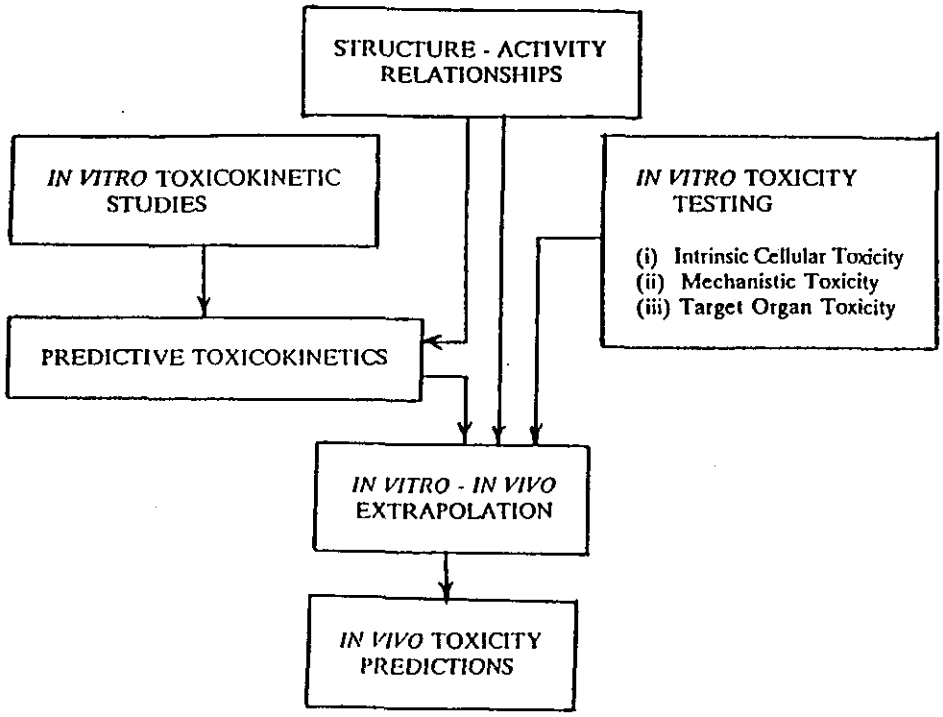


Figure 3 A proposed scheme for toxicological evaluations based on *in vitro* and computer technologies.

Limb bud cell culture for in vitro teratogen prescreening.

Junzo Yonemoto

National Institute for Environmental Studies, Tsukuba, Japan.

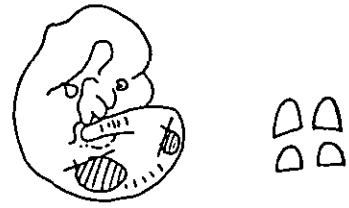
Although thre are no alternative test system which replace in vivo mammalian teratogenicity test because of diversity and complexity of the causes and outcomes of teratogenicity, the need for alternative test as a prescreening is enormous since the in vivo test is laborious, time-comsuming and expensive.

Among alternative tests developed so far, micromass culture of rodent limb bud mesenchymal cells (LBC) is one of the candidates for teratogenicity prescreening tests. LBC assesses cell differentiation and cell proliferation simultaneously which allows one to calculate a kind of "developmental hazard" estimate.

A validation study of LBC has conducted using metals and related compounds known to be teratogenic to mammalian experimental animals. Fifty percent inhibition concentration for cell proliferation (IP_{50}), 50% inhibition concentration for differentiation (ID_{50}) and the ratio of IP_{50} to ID_{50} (P/D ratio) were obtained from LBC. Among teratogens, P/D ratios were more than 3 except methylmercury, Ni and Li, while P/D ratios were around 1 among nonteratogens. Using the criteria of high P/D ratio and very low ID_{50}, LBC had shown to be useful for metals and related compounds to rank the priority for further teratogenicity tests.

Procedure for Limb Bud Cell Culture

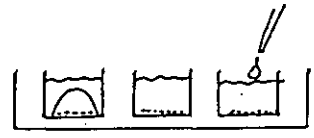
- Disect limb buds (Day 13 embryo)



- Dissociate into single cell with trypsin
- Adjust cell number to 2×10^7 /ml

- Deliver cell suspension in each well & allow to settle

- Flooded with medium
- Add test compound



- Incubate in CO_2 incubator for 7 days
- Stain with alcian blue for differentiation & with neutral red for cell proliferation

- Extract alcian blue with 4M guanidine-HCl & measure O.D. at 600 nm
- Extract neutral red with 50% alcohol (0.5% acetic acid) & measure O.D. at 550 nm

Panel 1. Procedure for limb bud cell culture.

Analysis of the Results

Dose-Response Analysis .....IC_{50}, IC_{10}

- Graphical
- Statistical ..... - linear regression
  - non-linear regression

Logit model:

$$q_i = \frac{1}{1 + e^{(\alpha+\beta x_i)}} + \varepsilon_i$$

- SAS PROC NLIN
- SALS

End Points:
- IC_{50} (ID_{50}, IP_{50})
- P/D ratio = IP_{50} / ID_{50}
- α: intercept
- β: slope

Panel 2. Procedure for the calculation of IC_{50} and IC_{10}

Validation study for metals and related compounds

Test compounds:

- Positive — As(III), As(V), Cd, Hg(II), Hg(MMC), In, Li, Ni
- Negative — Co, Ga, Se
- Positive control — Retinoic acid(*all-trans*)

End points:
- *in vitro* — IP_{50}, ID_{50}, IP_{50}/ID_{50} = P/D
- *in vivo* — LD_{50}, TDL_0, LD_{50}/TDL_0=A/D

Method: "Developmental hazard" approach

Panel 3. Materials and methods for validation study for metals and related compounds.

Table 1. Comparison of the IC_{50} values (IP_{50}, ID_{50} and their ratio) of metal compounds and retinoic acid in limb bud cell cultures with their *in vivo* data.

Chemicals		LBC			*in vivo*				
		ID_{50} (μM)	IP_{50} (μM)	P/D	Species	route	TDL_0 (μmol/kg)	LD_{50} (μmol/kg)	A/D
As(III)	$NaAsO_2$	3.4	11.8	3.47	mouse	ip(9D)	77.0 [9]	146.3 [10]	1.9
As(V)	Na_2HAsO_4	23.9	79.7	3.33	mouse	ip(9D)	128.2 [11]	233.0 *	1.82
Cd	$CdCl_2$	1.1	5.8	5.3	mouse	ip(10D)	21.8 [12]	50.7 [13]	2.3
Hg	$HgCl_2$	4.8	15.5	3.22	rat	iv(8D)	2.49 [14]	4.99 [14]	2.0
In	$In(NO_3)_2$	5.5	34.7	6.32	ham	iv(8D)	1.66 [15]	33.24~[15]	20~
Li	Li_2CO_3	100<	100<	-	mouse	ip(9D)	2710 [16]	5420 [16]	2.0
MMC	CH_3HgCl	0.40	0.06	0.15	mouse	po(10D)	59.7 [17]	220.4 [17]	3.84
Ni	$NiCl_2$	43.9	67.9	1.55	rat	ip(12D)	34.1 [18]	158.9 [18]	4.7
Ga	$Ga_2(SO_4)_3$	11.4	14.5	1.27	ham	iv(8D)	10.7 [15]	-	-
Co	$CoCl_2$	19.7	19.8	1.01	mouse	ip(10D)	192.6 [19]	377.4 [20]	1.96
Se	Na_2SeO_3	8.0	10.9	1.37	mouse	sc(12D)	40.0 [21]	58.7 [21]	1.47
RA	Retinoic acid all-trans	0.022	19.0	864	mouse	po(8D)	49.9 [22]	719 [23]	14.4

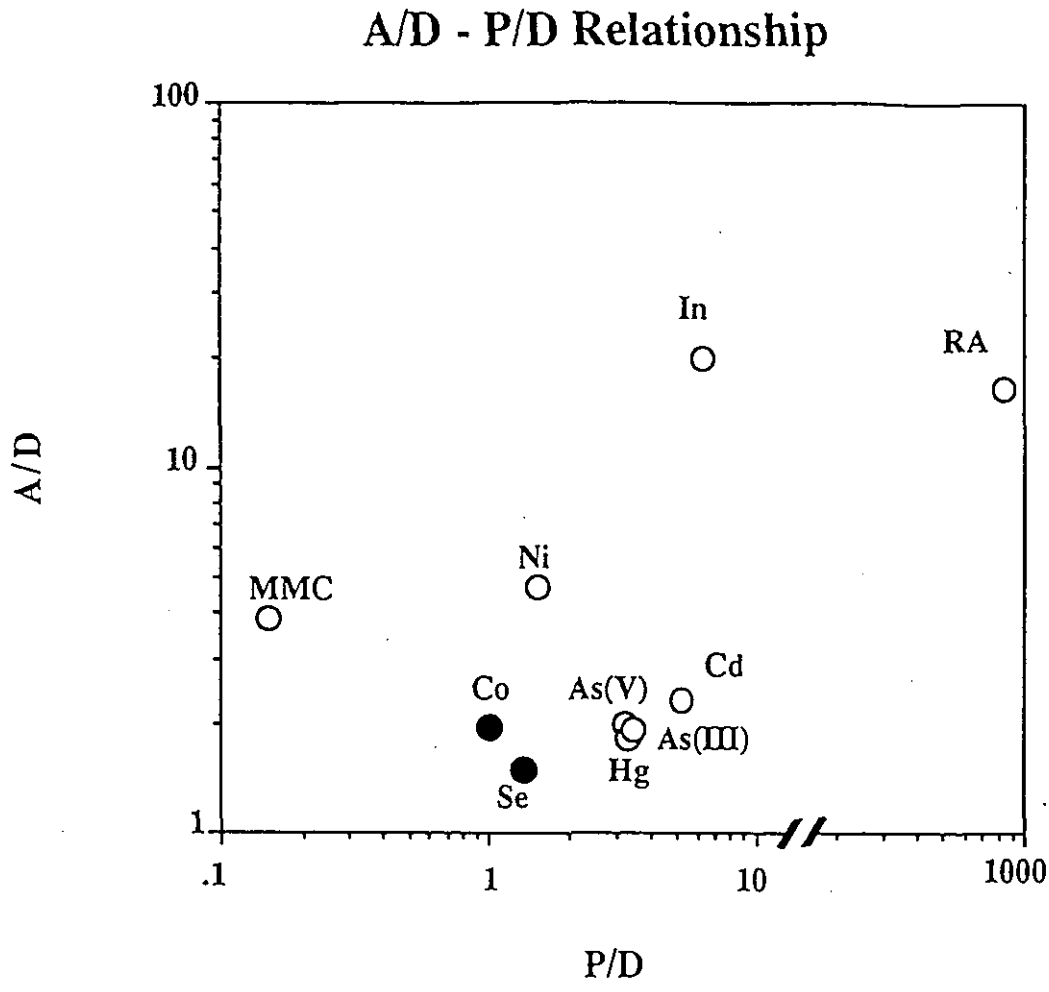


Fig. 1. The relationship between A/D ratio (LD_{50}/TDL_0)obtained from *in vivo* data and P/D ratio (IP_{50}/ID_{50}) from limb bud cell cultures among "teratogenic" (○) and "non-teratogenic" (●) metal compounds.

Table 2. Validation performance of limb bud cell culture for metals

	Criteria for classification *in vitro*			
	< 100 μM	< 10 μM	2-fold	3-fold
Compounds	11	11	10	10
Teratogen	8	8	7	7
Non-Teratogen	3	3	3	3
false negative	Li	As(V), Li, Ni	MMC, Ni	MMC, Ni
false positive	Ga, Co, Se	Se		
Sensitivity	7/8(88%)	5/8(63%)	5/7(71%)	5/7(71%)
Specificity	0/3(0%)	2/3(67%)	3/3(100%)	3/3(100%)
Accuracy	7/11(64%)	7/11(64%)	8/10(80%)	8/10(80%)

BASAL CYTOTOXICITY DATA (BC-DATA) IN HUMAN RISK ASSESSMENT

Björn Ekwall, M.D., Ph.D.
Dept. Toxicology, University of Uppsala
Box. 594, S-75124 Uppsala, Sweden

The animal data used routinely in risk assessment are not ideal due to species differences. New supplementary approaches are therefore welcome, such as toxicokinetic modeling and animal "scaling". In the last decades, the new in vitro methodology has contributed with data which can be used for risk assessment. First, the possibility to perform mechanistic studies in cell cultures with use of specialized cells from different species, including man, has increased precision in extrapolating animal toxicity to human conditions. Second, mechanistic short-term tests on bacteria and cells of mutagenicity and carcinogenicity can improve risk assessment of carcinogenicity. Third, the use of human hepatocyte, and to an extent rat hepatocyte, cultures is of great value in determining species differences in biotransformation.

However, the most powerful tool in risk evaluation contributed by in vitro toxicology will probably be the use of basal cytotoxicity data (BC-data). BC-data are toxicity in vitro of chemicals to cultures of non-differentiated cells such as finite or transformed cell lines. Diverse animal cell lines may be used, but the use of human cells is the method of choice. BC-data include various toxic parameters (IC10, IC50) determined after varying exposure times (1 minute, 1h, 24-168h, 4 weeks, etc.) with use of various toxicity criteria (determination of protein content of cultures, neutral red uptake, LDH-release, MTT, etc.). At present, the use of BC-data in risk assessment is not established for legal use, but results from ongoing research and validation point at a break-through for this use of BC data in the near future. The present paper will review the experimental evidence for a successful application of BC-data in risk assessment and will also discuss the potency of the BC-approach.

To realize the role for various in vitro test systems in toxicity testing (isolated receptors, primary cultures of specialized cells, and cultures of non-differentiated cell lines, respectively) it is of value to classify toxicity of chemicals to the human body in three cathegories: A. organisational toxicity to extracellular targets; B. Organ specific cell injury; and C. Basal cytotoxicity (BC), i.e. injury to the minimal, common denominator of structures (organelles, macromolecules, etc.) and functions of all cells in the human body, such as nucleus, cell membrane, ribosomes, mitochondria, etc.(1,2). Hypothetically, the

last type of toxicity, i.e. BC would represent a potential, maximal toxicity for all classes of chemicals. Furthermore, it would have the possibility to be experimentally measured in simple in vitro tests with non-differentiated cells. An open question, at the time for this theory, was if BC also would represent the actual human toxicity (the minimal injury) of a reasonable number of chemicals.

In the last decade, a large number of studies by the author (1,2) and other investigators (referenced in 3) have indicated the usefulness of in vitro BC for prediction of human toxicity. Generally, these studies have compared in vitro toxicity to cell lines with human and animal doses and concentrations involved in acute systemic toxicity, target organ toxicity, eye irritancy, skin irritancy, teratogenicity, and so forth. The BC data compared have most often been 24-72h IC50 (50% inhibitory concentration) for animal or human cells. Some of the results have been: 1. A good (75%) correlation in several studies involving hundreds of non-selected chemicals between cell line IC50 and rodent LD50. 2. A similarily good correlation between cell line IC50 and eye irritancy. 3. A good correlation, but not so good as for LD50 and eye irritancy, between cell line IC50 and skin irritancy, teratogenicity, immunotoxicity, etc. 4. A good correlation between various systemic target organ toxicities (nervous system, liver, kidney, etc.) and cell line IC50, indicating that most cases of target organ toxicity indeed is BC distributed to organs. 5. A very good corelation between cell line IC50 and acute human, lethal blood concentrations, for a limited number of compounds. 6. Several new studies have revealed that 24-48h IC50 to cell lines are very similar, irrespective of the type of cell line and the toxicity criteria used. 7. If physiologically cultured cells are used, and if true concentrations for IC50 are measured, IC50 will never overestimate human toxicity, i.e. give false positive results.

The studies indicate that: 1. BC-data may be economically measured by IC50 tests on human cell lines (with no need for sacrificing animals, as is done with primary cultures); 2. The BC-data seem to represent a maximal, potential toxicity for all chemicals, and, furthermore, represent the actual, human toxicity for a majority (80-90%) of nonselected chemicals; 3. The BC-data, plus toxicokinetic data, can predict most systemic target organ toxicity; 4. The BC-data can be used to model many different types of general toxicity; 5. Since BC-data represent toxic concentrations of chemicals in the blood and/or tissue fluids, toxicokinetics must supplement BC-data in prediction of target organ toxicity, toxic doses, and toxicity of metabolites. and 6. The BC-data can not account of organisational or organ-specific cell toxicities. Both of these types of toxicity are infre-

quently (10%) found to be involved in acute human toxicity of non-selected chemicals, however. Moreover, BC-data may be supplemented by in vitro tests on isolated receptors or organ-specific cells in primary cultures to cover a part of such false negative results of the cell line tests. - Actually, an analysis of differential toxicity between BC data and in vitro data for organ-specific cytotoxicity or organisational toxicity can be positively used to detect the two latter forms of toxicity (2).

BC-data are more suited for risk assessment than most of the conventionally used toxicity data. By use of human cells, the species gap is overcome. BC-data are easily and economically generated. One set of data may be used in assessment of many types of toxicity - probably BC is partly involved in all types of recognized chemical toxicity in humans. Likewise will one set of data be able to predict a variety of target organ toxicities. Finally, the strong point of BC-data is their ability to point out risk for (any) serious effects when compared with actual human concentrations of a chemical (while the weak point is to point out, together with toxicokinetic data, the exact type of target organ injury).

BC-data may be used alone in risk assessment, or be used in concert with other data. In similarity with other singular toxicity data, BC-data will result in a rather poor risk assessment when compared to human exposure only. However, a high BC-toxicity compared with exposure indicates risk, especially if the compound i absorbed well, is not detoxified and is unevenly distributed. A quite good risk assessment could be done with BC-data only, if these can be compared with human blood and tissue concentrations of a compound at adequate exposure levels. Such short-cut assessment, with avoidance of animal tests, toxicokinetic considerations and other possible sources of error is facilitated by modern, sensitive analytical chemistry, and will probably be a method of choice in future risk evaluation.

BC-data may be used as supplements to any set of conventional toxicity tests, to improve risk assessment. A comparison between BC-data and animal toxicity will result in information on the level of toxicity, i.e. if organisational, organ-specific cellular or basal cellular toxicity is involved. BC-data could also be used in concert with other in vitro data on toxicity and toxicokinetics, to build up non-animal models of human toxicity for comparisons with exposure, thereby circumventing the species gap. Such modelling would be necessary, if the short-cut approach cannot be applied, due to difficulties in getting samples of blood and tissue concentrations for actual exposure, etc.

There is already a base for the practical introduction of BC-data into the risk assessment process. However, the use right now of BC-data for this purpose requires a thorough understanding of in vitro toxicology by the user, and may also lead to initial, unacceptable variations in assessment between experts. Therefore, regulatory agencies and other concerned parties have to wait for more documentation and better standardization of BC-data, before general use. It is advisable, however, not to wait passively for the great potential improvement of risk assessment. Instead, regulatory agencies, etc. may alert themselves to BC-data. This can be done by the installing and use of simple cytotoxicology laboratories, providing the agency with BC-data on compounds assessed to be used provisionally along with the data provided by industry. This would lead to practical experience with in vitro cytotoxicity data, and will probably lead to enthusiasm for BC-data as well as the necessary insight into limitations of such data.

At present, many programs are in progress with the aim to validate, that is evaluate the relevance and reliability of in vitro cytotoxicity tests. One of these programmes, the Scandinavian-based MEIC (Multicenter Evaluation of In Vitro Cytotoxicity Tests) has a primary goal to evaluate the usefulness of BC-data (4). When these programs have been finalized within a couple of years new evidence on the utility of BC-data will be gained, including a selection of the best BC-tests. These tests may then be accepted by regulatory agencies as valid for use in risk assessment.

References

1. Ekwall, B. (1983) Screening of toxic compounds in mammalian cell cultures. Ann, N. Y. Acad. Sci., 407, 64-77.

2. Ekwall, B. & Ekwall, K. (1988) Comments on the use of diverse cell systems in toxicity testing. ATLA, 15, 193-200.

3. Ekwall, B., Bondesson, I., Hellberg, S., Högberg, J., Romert, L., Stenberg, K. & Walum, E. (1991) Validation of in vitro cytotoxicity tests - past and present strategies. ATLA, 19, 226-233.

4. Bondesson, I., Ekwall, B., Hellberg, S., Romert, L., Stenberg, K. & Walum, E. (1989) MEIC - a new international multicenter project to evaluate the relevance to human toxicity of in vitro cytotoxicity tests. Cell Biol. & Toxicol., 5, 331-348.

Session D

Risk Management

Integrated simulation model for health risk assessment

Robert G. Kellam (US EPA, USA)

ABSTRACT

Title III of the Clean Air Act of 1990 places new emphasis on the use of health risk assessment in the regulation of toxic air pollutants emitted from stationary industrial sources. Information on the extent of human exposure and potential magnitude of health risks from toxic emissions will be used to determine whether substances meet the criteria for listing as hazardous air pollutants, to establish priorities for the regulation of individual categories of industrial sources, and to assess whether technology-based emission standards are sufficient to protect public health with an "ample margin of safety". The principal assessment tool in this regard is the U.S. Environmental Protection Agency's (EPA) Human Exposure Model (HEM), an integrated computer simulation model that combines information on sources, emissions, meteorology, and populations to estimate levels of human exposure to toxic air pollutants. Exposure estimates are then combined with toxicological dose/response information, where available, to estimate chronic health risks. This paper describes the development and operation of HEM, its use in EPA's air regulatory program, and ongoing improvements to better support the implementation of the new Clean Air Act.

Introduction and Background

The HEM was developed in the early 1980's by EPA's Office of Air Quality Planning and Standards as a screening model in the identification and national assessment of candidate hazardous air pollutants under Section 112 (National Emission Standards for Hazardous Air Pollutants) of the Clean Air Act. This role expanded in the mid-1980's to include more detailed quantitative evaluation of health risks (principally cancer) associated with emission sources of hazardous air pollutants. The resulting estimates were used to support the development of specific national emission standards and to aid in the determination of whether such standards provided the required margin of safety to protect public health.

With the increased emphasis on quantitative estimation of risk, the HEM was evaluated in 1985 to identify needed improvements and to consider structural modifications to the model's software capable of accommodating foreseeable changes in risk assessment methods. The resulting modular design of HEM allows for revisions to be made more easily without affecting the integrity of the overall structure. The current HEM architecture permits the user to select the original screening model (HEM-I) or the more advanced model (HEM-II) as the available data or the purpose of the assessment dictate. The software architecture also provides for subsequent enabling of additional features (e.g. consideration of population mobility, migration) as information sufficient to characterize these parameters becomes available.

Current developmental efforts include the addition of a Monte Carlo shell to permit the representation of critical parameters as distributions rather than point estimates and the integration of HEM with Geographical Information System (GIS) data bases. The HEM is also under evaluation by the U.S. National Academy of Sciences as part of their study, required under the amended Clean Air Act, of EPA's air toxics risk assessment methodologies. The NAS report and recommendations for improvement are due in late 1993.

Description of the Model

The HEM is, in actuality, a collection of models, selectable by the user depending on the nature and magnitude of the assessment and the amount and quality of the input data. Several atmospheric dispersion models (e.g., ISCLT, CDM, TOXBOX) are incorporated into HEM. Alternatively, outputs from other dispersion models such as LONGZ can be input to HEM if provided in the appropriate format. HEM also contains extensive meteorological and census data bases to support the dispersion modeling of emissions and the estimation of population exposure.

For a given study, the user must supply sufficient information about the subject emission sources (e.g., location, source strength, etc.) to drive the appropriate dispersion model (Figure 1). Based on the location of the sources, HEM selects representative meteorological data from its internal data base for the dispersion modeling and population data from the census data base to use in the exposure calculations. The dispersion model estimates the long-term, annual average concentration of the emitted pollutant(s) in the vicinity of the sources. This information is overlaid with the census data to obtain estimates of population exposure. The population exposure estimates are combined, in the case of carcinogens, with a measure of carcinogenic strength (unit risk estimate) to provide estimates of expected cancer risk.

Dispersion Modeling

The original HEM contained a dispersion model based on EPA's Climatological Dispersion Model (CDM), a simplified, steady-state Gaussian plume model. While this model remains available for screening studies, it has been largely replaced in the current version by the EPA Industrial Source Complex Long-Term (ISCLT) model. The ISCLT is also a climatological model but offers several advantages over the version of CDM, in particular the ability to locate individual point and fugitive sources within a plant boundary rather than assume that all emissions occur at the plant center. Area sources such as gasoline stations, that are characterized by numerous diffuse sources of emissions and are difficult to locate, are modeled in HEM by use of the Hanna-Gifford box model or the TOXBOX model adapted from EPA's Office of Toxic Substances Graphic Exposure Modeling System.

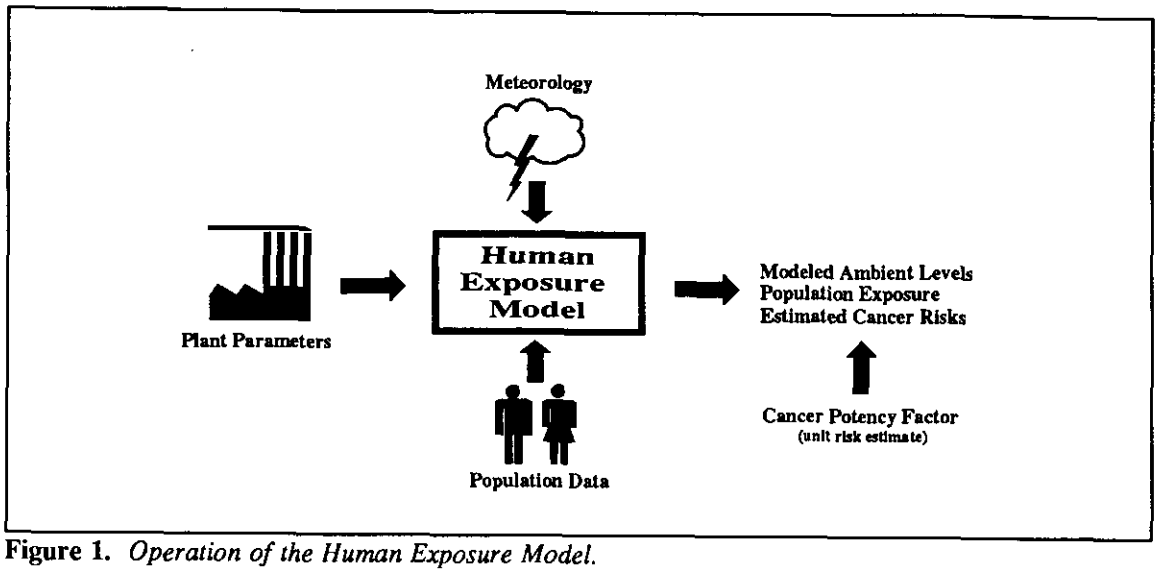


Figure 1. *Operation of the Human Exposure Model.*

For a model such as the ISCLT, the HEM user must specify the location of the source or emission point (latitude and longitude), emission rate, and other information about the release (e.g., release height, stack gas temperature, exit velocity). The area source box models assume uniform dispersion of emissions from sources located in a given area, with TOXBOX offering the additional consideration of removal by dry deposition or precipitation.

Meteorological Data Base

The dispersion models in HEM require meteorological data in order to perform the required calculations. The meteorological data in HEM originate from the National Weather Service Stability Array (STAR) data, expressed as the joint frequency occurrence of wind speed and direction by atmospheric stability class. There are approximately 300 STAR sites in the U.S., normally located at airports. The HEM selects the nearest STAR site to the source being modeled. Due to local meteorological conditions and topography, however, the closest STAR site may not be representative of the source location. In such cases, the user may select another STAR data set manually.

Population Data Base

The population data in HEM are derived from the U.S. census data base. In the 1980 U.S. census, the finest level of disaggregation is the Block Group/Enumeration District (BG/ED). In cities, a Block Group is roughly the area covered by several city blocks. Enumeration Districts are more characteristic of rural areas, contain fewer than 10,000 people, and can vary substantially in size depending on population density. There are approximately 300,000 BG/EDs in the 1980 census. For each BG/ED, HEM can access the population count and the latitude and longitude of the population-weighted centroid of the BG/ED.

The preliminary results of the U.S. 1990 census are now available and are being incorporated into HEM. The 1990 data will provide a greater degree of resolution, both in the physical location of populations and in their make-up. With the introduction of GIS, the boundaries of census tracts will be retrievable, providing a greater degree of accuracy in locating populations near emitting sources. Better distinction will also be possible with regard to sex, age, economic status, and transportation patterns, to the extent such parameters may affect the estimation of health risks.

Exposure Calculation

The point source dispersion models in HEM calculate pollutant concentrations at the intersections of a receptor grid. For modeling a single facility, the grid of choice is usually a polar coordinate grid with 16 radials and 10-15 concentric rings at user-specified distances from the center (Figure 2). The intersections of radials and rings form the grid of receptors at which ambient long-term average concentrations are estimated.

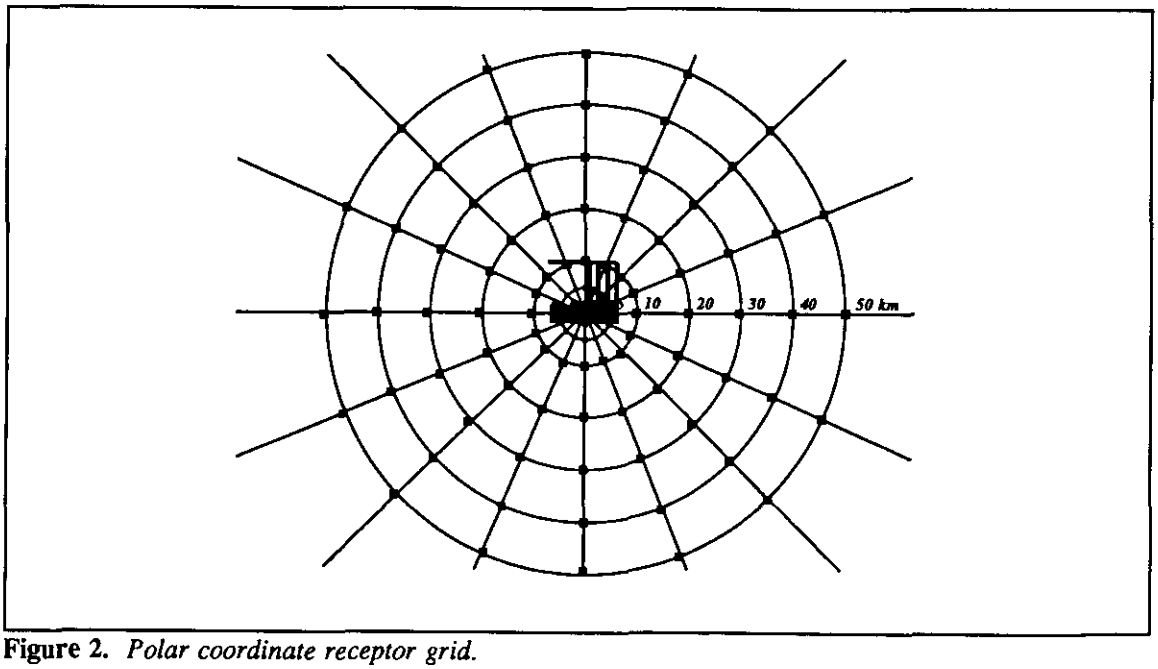


Figure 2. *Polar coordinate receptor grid.*

To estimate population exposure, HEM retrieves the data for all BG/EDs with centroids located within the study area (usually a 50 kilometer radius from the source). The model has two means of matching populations with predicted concentrations. For BG/EDs greater than 3.5 kilometers from the source, the model interpolates a concentration for the BG/ED using the predicted concentrations at the four receptorsthat bound the BG/ED centroid (Figure 3). The population of the BG/ED are assumed to be exposed at the level of the interpolated concentration.

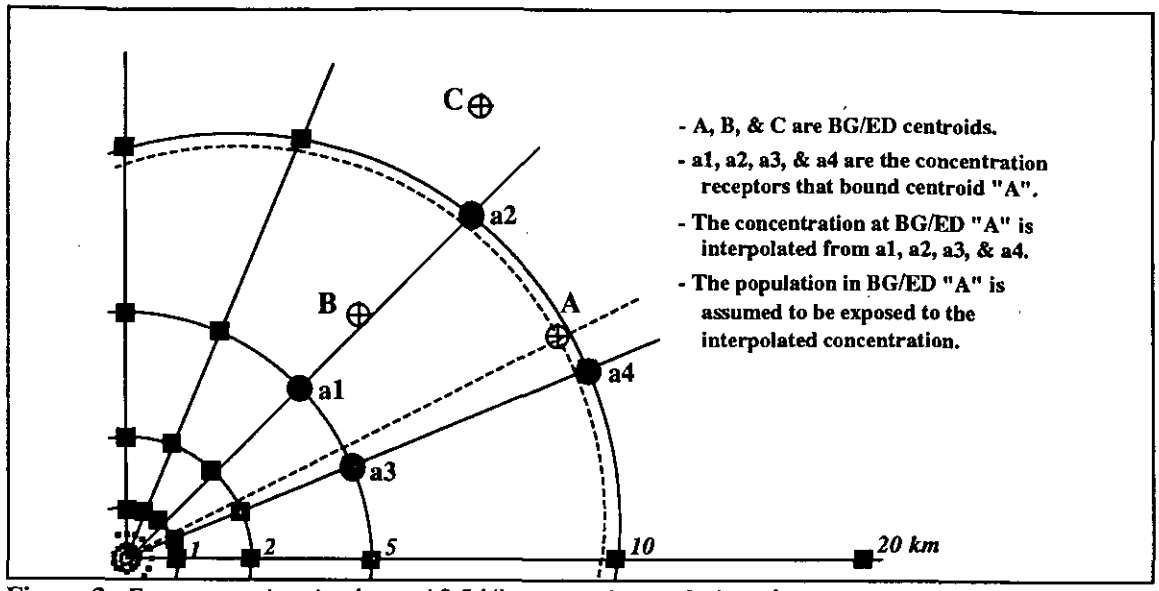


Figure 3. *Exposure estimation beyond 3.5 kilometers: interpolation of receptor concentrations to BG/ED centroids.*

Closer to the source (within 3.5 kilometers), the model, instead, apportions the population of a given BG/ED to all receptors that are closer to that BG/ED centroid than any other centroid (Figure 4). The population assigned to a given receptor are assumed to be exposed at the concentration predicted at the receptor. The fraction of the BG/ED's population assigned to a given receptor is proportional to the area ascribed to that receptor. In a polar receptor grid, receptors closer to the source receive a proportionally smaller share of the population since they "represent" smaller pieces of the study area. This method is consistent with the assumption that the population is uniformly distributed.

The change in calculation method close to the source reflects the concern that a relatively steep concentration gradient exists close to most emitting sources and the location of the nearest BG/ED centroid represents, by its definition as the population-weighted center, an underestimate of the highest predicted concentration to which some segment of the population could be exposed.

The current version of HEM also allows for the specification of a Cartesian (rectangular) grid for more efficient calculation in densely populated areas. In this implementation, each grid cell acts as a pseudo-BG/ED with a population equal to the sum of all BG/EDs with centroids in the cell, and with the concentration receptor located in the geographic center of the cell.

Risk Characterization

For a given HEM study, exposure is reported as the size of the population exposed within a number of concentration intervals (e.g., 18,000 exposed to a range of

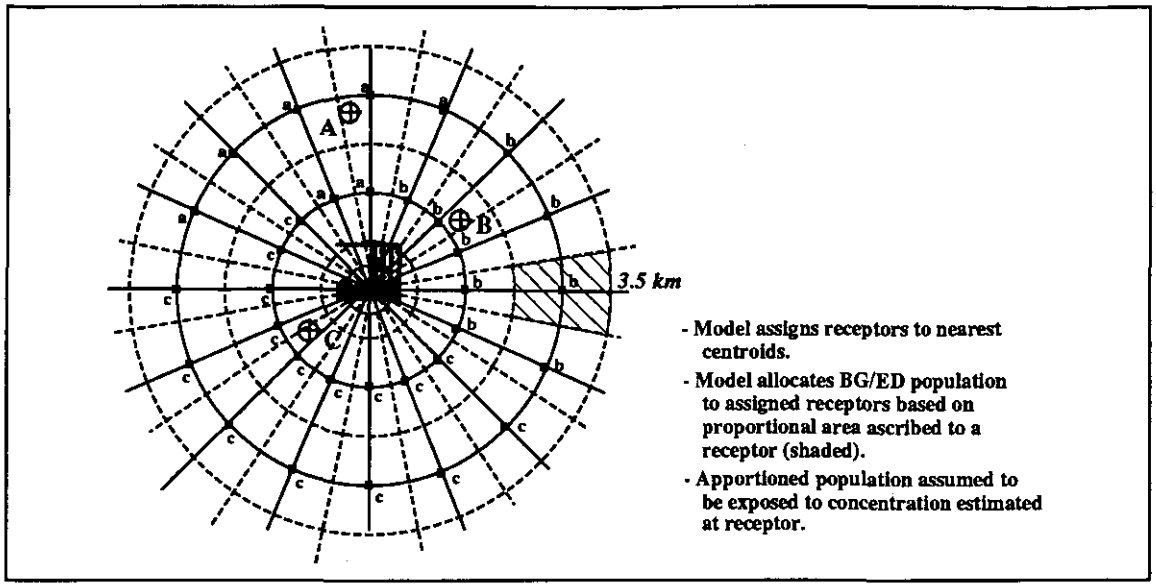


Figure 4. *Estimation of exposure within 3.5 kilometers: apportionment of population to receptors.*

2.5-5.0 $\mu g/m^3$; 40,000 exposed to 5.0-7.5 $\mu g/m^3$; etc.). If toxicological dose\response information is sufficient, estimates of expected health risk can be calculated.

For carcinogens, the measure of carcinogenic potency is the unit risk estimate, usually expressed as the probability of contracting cancer as the result of lifetime exposure to a unit concentration (e.g., 1 $\mu g/m^3$). The combination of the unit risk estimate with exposure estimates derived from HEM, allows the estimation of excess cancer risks associated with emissions of carcinogenic air pollutants. For a particular assessment, three measures of cancer risk are estimated: maximum individual lifetime risk (MIR), distribution of individual risk, and population risk.

The MIR is the estimated probability of contracting cancer associated with lifetime exposure at the maximum predicted, long-term, ambient concentration. The MIR usually occurs at a receptor close to the source and is very sensitive to emissions, meteorology, distance to the nearest residence, and population assumptions. The risk distribution represents the distribution of individual lifetime risk across the exposed population in the study area (e.g., within 50 kilometers). The distribution is usually presented as the magnitude of the exposed population within selected risk intervals. Population risk is the sum of the individual risks across the exposed population, usually expressed as the expected annual incidence of cancer (cases per year). Table I. illustrates the risk results for a hypothetical category of benzene sources.

Although most HEM applications to date have focused on known or suspected airborne carcinogens, the model can also be used to estimate exposure to other chronic toxicants. Estimation of risk, however, requires sufficient toxicological data to

Risk Characterization: Benzene Coke By-Product Plants

Maximum Individual Risk (MIR):

Before control: 7×10^{-3}
After control: 2×10^{-4}

Distribution of Individual Risk:

exposed population before control	*individual risk interval*	*exposed population after control*
4,000	$> 10^{-3}$	0
96,000	10^{-4}- 10^{-3}	200
2,900,000	10^{-5}- 10^{-4}	20,000
27,000,000	10^{-6}- 10^{-5}	380,000
60,000,000	$< 10^{-6}$	89,500,000

Population Risk (expected annual incidence):

Before control: 2 cases/year
After control: 0.05 cases/year

Table I. *Example of HEM exposure and risk results for a hypothetical category of benzene sources. (Does not include uncertainty discussion which routinely accompanies presentation of results).*

characterize the relationship between dose and response. These data are often lacking for noncancer health endpoints.

Assumptions and Uncertainties

It is important to note that the use of the current version of HEM in the assessment of human exposure to air toxic emissions requires a number of default assumptions. The need for such assumptions stems from the complex nature of this interaction, the practical limits on the collection of supporting technical data, and the gaps in our understanding of the relevant health science. In the latter area, one of the most important, and controversial, assumptions for airborne carcinogens has been that cancer is a non-threshold effect with a linear dose/response relationship in the low dose region. Other default assumptions in HEM include: that ambient air is the only source of exposure to industrial emissions, that emissions are continuous, that exposure is lifelong, that the exposed population is immobile, and that the point of predicted maximum concentration is ambient air and habitable.

The use of default assumptions in HEM may, depending on the assumption, lead to the under- or overestimation of actual exposure and risk. While the elimination of such assumptions is not feasible, a considerable part of the ongoing work in HEM development, described briefly in the following section, is directed at better understanding and improving consideration of exposure parameters (e.g.,

exposure duration, population mobility, indirect exposure) that may have a significant impact on the levels predicted.

Sources of scientific and technical uncertainty in HEM exposure and risk estimates include: 1) the likelihood that the identified health effects will occur at predicted ambient levels; 2) the extent to which all relevant health endpoints have been considered in the analysis; 3) the quality and representativeness of the emissions data and other plant-specific parameters; 4) the accuracy of the source locations and boundaries; 5) the coarseness of the census data; 6) the appropriateness of the selected meteorological data set; and 7) the impact of complex terrain in situations where a flat terrain model is used for dispersion analysis. Because such uncertainties may be substantial, HEM assessments are accompanied by, at a minimum, a qualitative discussion of the inherent scientific and technical uncertainties present. Also, in recognition of the inherent uncertainty, HEM estimates are generally regarded as better relative indicators of exposure and risk than as absolute estimates.

Applications and Current Development

Exposure modeling will serve a number of purposes in the implementation of the new Clean Air Act. In a screening capacity, HEM is being used in the ranking of source categories for standards development and in the identification of "high risk" subsets of the list of hazardous air pollutants for which certain limitations (weighted trading in early reduction demonstrations) or alternative major source definitions (lesser quantity emission rates) may apply.

HEM will also be used in both screening and site-specific modes in the evaluation of petitions to add or delete compounds from the list of hazardous air pollutants, and in petitions to delete source categories from the list scheduled for regulation development. In both cases, the law requires consideration of exposure and/or risk in a petitioner's demonstration that the criteria for addition or deletion have been met.

Finally, HEM will play a major role in the evaluation of residual risks after the application of technology-based emission standards. This provision of the Act requires that further standards be established if the risks associated with residual emissions from sources in a regulated category exceed a lifetime risk of 1 in 1 million (1×10^{-6}) or do not provide an "ample margin of safety" to protect public health or the environment.

In view of the requirement for residual risk evaluation, and the emphasis that this requirement places on source-specific analysis, much of the current development work on the exposure components of HEM is intended to reduce reliance on default assumptions and improve the characterization of uncertainty. Similar work is also underway within EPA's Office of Research and Development to evaluate and improve methods for deriving toxicological dose/response relationships (e.g., unit risk estimates

for carcinogens) based on available science.

With regard to the default assumptions in HEM, major emphasis is being placed on evaluating the feasibility of incorporating Geographic Information System (GIS) technology to improve the assessment and graphical display capabilities of HEM. A GIS is a software system that retrieves, analyzes, and displays spatial information. The 1990 U.S. census data, for example, include GIS files containing census block group boundaries. GIS enables such files to be overlaid on an HEM study area, offering a higher resolution in the location of populations than that offered by the current BG/ED centroids.

A second major emphasis in HEM development is the provision of stochastic processing capability. The model currently operates in a deterministic mode only, requiring discrete values for input parameters that may be inherently uncertain (e.g., emission magnitude, exposure duration, distance to nearest residence). An advanced feature now in application testing allows the specification of critical parameters as distributions rather than point estimates. A Monte Carlo SHELL is fitted around the dispersion algorithm and provides for sampling from the specified distributions in the course of running a Monte Carlo simulation. Outputs from the model are also displayed as distributions with confidence intervals.

As noted above, the present HEM as well as ongoing efforts to improve the model, are a principal focus of the National Academy of Sciences (NAS) study of EPA's air toxic risk assessment methodologies. The NAS' recommendations, due in the form of a report to Congress in late 1993, will provide additional opportunity for improvement of the model prior to the initiation of the residual risk evaluations late in the decade.

Supplemental References

1. **Human Exposure Model: Users' Manual.** Office of Air Quality Planning and Standards, U.S. EPA, June, 1986. (EPA 450/5-86-001)

2. **Technical Support Manual for the Human Exposure Model.** (Review Draft) Office of Air Quality Planning and Standards, U.S. EPA, December, 1991.

3. **HEM-II User's Guide.** Office of Air Quality Planning and Standards, U.S. EPA, January, 1992. (EPA 450/3-91-0010)

HEALTH RISK ASSESSMENT/MANAGEMENT OF PESTICIDES - PRINCIPLES AND METHODS

Jun Sekizawa

(National Institute of Hygienic Sciences)

INTRODUCTION

There have been dramatical changes in food supply of Japan in these decades. First, infrastructure of agricultural production was changed very drastically. Percentages of people who engage in agriculture in total labour force decreased from 38% in 1955 to 9.8% in 1980 and further decreasing recently. Not only that, but also higher percentage of elder people are working in agriculture now as compared to before. This makes our agriculture depends much to machines and agrochemicals including pesticides (Table 1). The situation incurs higher potential risks among farmers who use pesticides, risks for consumers from pesticide residues in foods and the various impacts to the environment.

Another change in food supply of Japan is increasing dependence to import of foods and food materials (Table 2). Apparently, there is a striking difference between Japan and other major advanced countries in the policys of governments for supporting its own food supply. Since regulations of food contaminants including pesticide residues vary among countries, it is required to understand or harmonize in some cases, the regulations internationally to protect food safety in Japan.

Table 1 Changes in Food Supply in Japan

Dramatic decrease of farmers &
higher percentage of elder farmers
—> Saving of man power
Use of pesticides & machines
Import of huge amount of food materials
—> Need for checking safety and
quality of imported foods
Need for information exchange

Table 2 Self Supply of Foods in Advanced Countries (calorie base)

USA	127% *	France	128% (1983)
Netherland	98% *	West Germany	93% *
United Kingdom	77% *	Japan	49% (1987)

* (1985)

From White paper on food (1990)

From this recognition, I want to discuss basic matters in risk assessment (especially in health) and risk management on pesticides. First, I will overview current risk assessment/management systems on pesticides. Second, I will discuss several problems in principles and methods of risk assessment/management on pesticides and propose some improvements based on my studies. Namely, I will make use of outputs from my database on pesticides to analyze the situation of pesticide use in Japan and then show result of a trial of mechanistic approach in assessment of carcinogenic risk from pesticide residues in foods.

CURRENT RISK ASSESSMENT/MANAGEMENT ON PESTICIDES

(1) Risk assessment by international organizations

Possible risks from pesticide use are summarized in Table 3.

Table 3 Possible Risks from Pesticide Use

Types of Risks	Targets
Health Risks	
Residues in foods	General population
drinking water, air	Habitant
Occupational exposure	Farmers, Workers
Environmental Risks	
Toxic effects	Organisms in the environment ex) birds, fish, insects microorganisms
Function & quality	Properties of soil Ecological balance etc.

International cooperation in assessment/management of health risks from pesticides use have been performed inter alia in several United Nations bodies (Table4), such as the World Health Organization (WHO) and the Food and Agriculture Organization (FAO). Some aspects, such as carcinogenic risk is evaluated by the International Agency for Research on Cancer (IARC) and the risk in transportation is dealt by the International Maritime Organization (IMO). The International Programme on Chemical Safety (IPCS) summarizes and evaluates information on potential risks of chemicals including pesticides to health and environment.

WHO in collaboration with FAO deals with safety in pesticide residues in food through works of the Joint Meeting on Pesticide Residues (JMPR) and the Codex Committee on Pesticide Residues (CCPR). Acceptable Daily Intake (ADI) of pesticide residues is determined by JMPR through evaluation of No-Observed-Adverse-Effect Level (NOAEL) derived from all available toxicological information.

Table 4 International Programmes for Risk Assessment of Pesticides

Aim or Scope	Organization	Output
Safety evaluation of pesticide residues	JMPR/CCPR (FAO/WHO)	ADI MRL
International transport	IMO	Classification Packaging
Carcinogenic risk	IARC	IARC monographs
Evaluation of effects on health and environment	IPCS	Environmental Health Criteria

Maximum Residue Limit (MRL) is determined from residue data obtained in concordance with Good Agricultural Practice. The evaluations are based on information, not only published, but also unpublished one from governments or proprietary one from industries which are collected from all over the world. WHO also classifies pesticides based on acute toxicity.

The process and outputs of these evaluations are not always easily searched by the people who want to use them. I developed a database which helps searching these precious information and show some analysis of risk assessment/management of pesticides in Japan.

(2) Current pesticide regulations in Japan

Pesticides are regulated by several laws under several ministries and a agency in Japan. Pesticides (formulations) are registered by examinining data-set listed in Table 5.

Residue limits in foods are established and designation as pesticides which are water polluting, long-remaining in soil or in crops is determined for specified pesticides under the Agricultural Chemicals Control Law and the Food Sanitation Law. Sales, storage and handling are controled by the Poisonous and Deleterious Substances Control Law for acutely toxic pesticides. These information on management of pesticides are also put into the above mentioned database.

(3) Principles and methods in health risk assessment of pesticides

A recent publication of IPCS (1990) summarizes the principles and methods of toxicological assesssment of pesticide residues in food. Although many countries have their own procedure for risk assessment of pesticides, the basic ideas expressed in the IPCS publication are mostly internationally agreed. Major explicit difference in health risk assessment between JMPR and US-EPA procedure can be noted as use and non-use of mathematical models for assessment of carcinogenicity risk. JMPR prefers case-by-case approach to mathematical models.

Table 5 Information required for Pesticide Registration excluding administrative matters

Name and formulation type
Physicochemical properties
Active ingredients/Other ingredients and their composition
Container & packaging
Efficacy/Adverse effects on crop and use method
Hazards to human and cattles
Therapy of poisoning
Effects on aquatic organisms
Potential of explosion and flushing
Precaution for storage and use
Toxicological information
Acute toxicity : oral, dermal, inhalation
Primary irritation : skin, mucous membrane
Skin sensitization
Neurotoxicity : acute, delayed
Subchronic toxicity
Chronic toxicity
Carcinogenicity
Reproductive effects
Teratogenicity
Mutagenicity
Kinetics and metabolism
Functional effects
Residual potency on crop
Residual potency in soil

PROBLEMS IN CURRENT PROCEDURES

(1) Animal studies

Current health risk assessment depends mostly on data obtained from toxicological studies performed using animals. However, there are many obstacles in this approach.

(a) Many crucial data are obtained through a chronic or carcinogenicity study and various kinds of special toxicity studies which require huge amount of moneys/laboratory animals/expertise/years.

(b) There is not a satisfactory method for extrapolting animal data to man.

(c) Recently, acute toxicity studies, such as to obtain LD50 or to assess eye and skin irritation, using animals are the target of animal protection movement.

All these give toxicological assessment difficulties in obtaining satisfactory, pertinent data. Establishment of method and database for risk assessment of combined effects from mixtures used in current pesticide formulations is urgently required.

(2) Human studies

Most important information in health risk assessment is human data. Although many pesticides are in long, world-wide use, human data are relatively scarece.

(3) Environmental studies

There seems to be various dynamic aspects in the area of environmental studies. Environmental fate studies and effects on the organisms in the environment and the quality of the environment must be elucidated, not only by laboratory study and field survey but also by gross, dynamic analysis of function and quality of total environment. Only limited data are available on residues in food, water, air, soil and organisms.

APPROACHES TO SOLVE PROBLEMS

(1) Macroscopic and continuous approach

Large scale and long-ranged analysis of the effects are necessary to discover changes in the quality and function of human health and environment which are sometimes influenced by many disturbing factors.

Fig. 1 shows historical trend in the use of various pesticide formulations in Japan (not shown in the abstract).

Table 6 summarizes estimation of total consumption of high-volume-consumption pesticides (see Table 6 for definition) in Japan from 1975 to 1989 (pesticide year) as estimated from statistics on production, import and export of active ingredients in my database. Note that statistics on formulations are not included in estimation of consumption values, because amounts of pesticides in the formulations are hard to be examined from statistic figures.

Fig 2 shows historical trend of consumption of several pesticides (not shown in the abstract). Fluctuation seems to depend mostly to the timing of statistics as compared to timing of reports of production, import and export. However, the trend of consumption of major pesticides in Japan can be traced.

Table 7 lists structural features, use, regulations of high-volume-consumption pesticides. Fungicides, nematicides, insecticides and herbicides which are used mostly for fumigation of soil and in warehouses are ranked high. There are 11 organochlorine pesticides among 41 high-volume-consumption pesticides listed, which are considered to generally remain longer in the environment. The consumption of chloronitrofen which is known to contain little amount of polychlorinated dibenzodioxins is decreasing, but more than 43 tons were estimated to be used in the field of Japan in 1975-1989. The consumption of paraquat which is errouneously used for successful suicide attempts (several hundreds deaths per year) is decreasing, but still several hundreds tons are used per year. Residue limits for crops are not yet established for 9 pesticides among them.

Table 8 (not shown in the abstract) lists ADIs established by JMPR, WHO classification by acute hazards and evaluations by IPCS and IARC. ADIs are not evaluated for pesticides either when the pesticide is not used in many countries or toxicological information is not enough for

Table 6 Total Consumption Data for High-Volume-Consumption Pesticides*

Commonname	Total consumption** (kl/kg)
DICHLOROPROPENE	87086
CHLOROPICRIN	81354
METHYL BROMIDE	79009
THIOBENCARB	70442
FENITROTHION	54564
CHLORNITROFEN	43510
THIOPHANATE-METHYL	36849
IPROBENFOS	27721
SODIUM CHLORATE	26862
CHLOROTHALONIL	25814
FENOBUCARB	24478
DIAZINON	24475
EDIFENPHOS	21049
FENTHION	20094
ETHYLENE DIBROMIDE	19260
CARTAP	17258
QUINTOZENE	16760
ISOPROTHIOLANE	16562
MOLINATE	16204
COPPER SULFATE, BASIC	16114
DICHLORVOS	14174
CARBARYL	13764
MANEB	13625
TETRACHLOROPHTHALIDE	13195
CHLOMETHOXYFEN	13169
DISULFOTON	12825
BUTACHLOR	12561
CAPTAN	12090
TRICHLORFON	12057
PARAQUAT	11504
SIMETRYN	9878
PYRAZOLATE	8545
PHENTHOATE	8225
SETHOXYDIM	6222
SULFUR	4909
PENTACHLOROPHENOL	4906
MANCOZEB	4604
EPN	4304
FENVALERATE	3992
SWEP	3488
ISOPROCARB	2126

* At least once produced, imported or exported over 1000 kl/kg in a pesticide-year

** Sum of production vol. + import vol. - export vol. in 1975-1989

Table 7 Structural features, uses and regulations in Japan

COMMONNAME	STRUC *1	USE *2	RES *3	POISON *4	FISH *5
DICHLOROPROPENE *	OC	IN NE			B
CHLOROPICRIN	OT	IN FU		dele	C
METHYL BROMIDE *	BR	IN NE		dele	A
THIOBENCARB	CB	HB	+		B
FENITROTHION	OP	IN	+		B
CHLORNITROFEN	PO OC	HB	+		A
THIOPHANATE-METHYL	CB	FU	+		A
IPROBENFOS	OP	FU	+		B
SODIUM CHLORATE *	OT	HB		dele	A
CHLOROTHALONIL	OC	FU	+		C
FENOBUCARB	CB	IN	+	dele	B-s
DIAZINON	OP HC	IN AC	+	dele	B-s
EDIFENPHOS	OP	FU	+	dele	B
FENTHION	OP	IN	+	dele	B
ETHYLENE DIBROMIDE *	BR	IN NE		dele	
CARTAP	TC	IN	+	dele	B-s
QUINTOZENE	OC	FU	+		A
ISOPROTHIOLANE	OT	IN FU	+		B
MOLINATE	CB	HB	+		B
COPPER SULFATE, BASIC	CU	FU			B
DICHLORVOS	OP OC	IN AN	+	dele	B
CARBARYL	CB	IN	+	dele	B
MANEB	TC	FU	+		B
TETRACHLOROPHTHALIDE *	OC	FU	+		A
CHLOMETHOXYFEN	PO OC	HB			B
DISULFOTON	OP	IN AC	+	pois	B
BUTACHLOR	AM	HB			B
CAPTAN	OC HC	FU	+		C
TRICHLORFON	OP OC	IN	+	dele	B
PARAQUAT	HC	HB	+	pois	A
SIMETRYN	TZ	HB	+		A
PYRAZOLATE *	HC OC	HB	+		B
PHENTHOATE	OP	IN	+	dele	B-s
SETHOXYDIM	OT	HB	+		B
SULFUR *	OT	AC FU			A
PENTACHLOROPHENOL *	OC	HB FU		dele	C
MANCOZEB	TC	FU	+		B
EPN *	OP	IN AC	+	pois	B-s
FENVALERATE	PY	IN	+	dele	C
SWEP *	CB OC	HB	+		B
ISOPROCARB	CB	IN	+	dele	B

*1 Structural features
*2 Uses
*3 Residue control in foods
*4 Control of sales/handling etc
dele :deleterious substance
pois :poisonous substance
*5 control for use to protect aquatic organism

evaluation. To my regret, ADIs established in Japan are not publicably available that I can not discuss about them here.

However, the outputs of the database clearly show the current status of risk assessment/management on pesticides and also tells future needs for risk assessment/management.

(2) Mechanistic approach

First, reasonable and realistic considerations are needed. I will show an example of risk (carcinogenic and non-carcinogenic) estimation of some pesticide residues in foods by combining analytical data on total dietary intake of pesticide residues in foods and drinking water (Table 9, not shown in the abstract) and several health effects criteria. In the course of discussion, clear descrimination of initiating & promoting effects in carcinogenic risk assessment will be proposed.

Second, indentification of critical effects, sensitive organs, and sensitive populations etc. are very important.

Third, one of the most important things is that how to evaluate the risk from multiple exposure. Taking into account of mechanistic consideration for the specified target organ, I will show an example of risk estimation from multiple exposure of pesticide residues.

Table 10 (not shown in the abstract) shows the result of estimation of risk of ordinary Japanese people on taking pesticide residues from foods and drinking water. It was estimated in comparison of uptake values deduced from analyses of materials shown in Table 9 and ADIs for pesticide residues or some carcinogenic potency factors. We can see 10^{-1} to 10^{-4} levels of risks in comparison to ADIs and 10^{-4} to 10^{-7} levels of risks in comparison to carcinogenic potency factors. Risks estimated in comparison to ADIs shows that there will be no significant problem for ordinary people at this moment. However, the carcinogenic risks estimated in Table 10 requires further consideration. In many carcinogenic potency factors and mathematical models currently used for carcinogenic risk assessment, it is generally accepted that there is no threshold values. This leads to the idea of the virtually safe dose (VSD) which is not easily apprehended by the ordinary people and sometimes invites dispute, such as, whether 10^{-5} or 10^{-6} risk is acceptable or not. However, if we see the matter more closely, there are many cases in which substances are likely to be working as promoters for carcinogenesis. Promoters work to cause accumulative effects that there could be thresholds in their effects. Evidences suggest that several organochlorine pesticides are workig as promoters in animal carcinogenesis. Until recently, it was not easy to detect putative threshold values in animal carcinogenicity tests which require abundant animals and long time. Hence people will not try to examine many doses at which no effect levels can be observed as compared to control. However, recent progress in animal carcinogenesis assay made it possible at least partly in a medium-term test which detects

liver preneoplastic foci in rats. When I searched reports which make use of this system, there are several which clearly describe thresholds. If we know the concentration of critical substances in the critical organ in man, we can extrapolate risks from threshold values obtained in animal tests for same substances in the same organ. Table 11 (not shown in the abstract) shows an example of this risk estimation.

Further to this, assuming that the effects of substances which exert hazard through same mechanism to the same critical organ can be considered as additive in certain conditions, we can estimate the risk from multiple exposure to chemicals. Table 12 (not shown in the abstract) explains this example.

As shown in these examples, we can estimate carcinogenic risks of multiple pesticide residues in more realistic and more comprehensive ways as compared to mechanical application of certain mathematic models or carcinogenic potency factors. Although above mentioned method is not applicable to every kind of substances currently, I think more efforts should be endeavoured in this direction (i.e., mechanistic approach).

(3) Identification and integration of critical information for the assessment

Data which are critical but missing must be identified. As shown in fore mentioned examples, integration of important data for risk assessment/management is imperative.

PROPOSALS

(1) Monitoring of health effects

In this context, some examples and recommendations from Environmental Health Criteria for several pesticides will be shown.

(a) Periodical monitoring of health conditions of people who are exposed to pesticides occupationally must be useful not only for protection of health of farmers and workers, but also detection of possible effects (eg. chronic, immunological) which may be otherwise difficult to be found.

(b) After spray inspection of sensitive populations (eg. pregnant women, children, aged people working or living closely to the sprayed area) must be performed.

(c) After spray measuremwnt of surrounding environmental media is highly requested to properly assess the relationship of exposure to pesticides and effects that might be detected.

(2) Data requirement

Special precaution for pesticide use in green-houses (residues, health effects and possible exposures) will be needed. Special data on this use must be required for formulations used in the green-houses.

From various reasons, formulations of mixtures of pesticides are used in actual use. Toxicological data for

these mixed formulations must be requested especially in cases when additive or synergistic effects are considered to be likely. In a similar manner, not only Good Agricultural Practice scenario but also possible worse-case scenario must be taken into consideration in the risk assessment in some cases.

(3) Comprehensive and protective management

(a) Many fatal cases induced by paraquat urge prohibition or at least severe restriction of its use.

(b) Especially for elderly people, clear and simple labelling, instructions and easy to perform protective measures must be provided.

(4) Risk communication

Enough information and understanding of risks in proper ways are the basis for protection of health and environment. Efforts to summarize the outputs of various researches and to propose clear ideas out of them for people who need proper information are extremely important to make risk management effective.

Health Risk Assessment of Drinking Water Contaminated by Herbicides and Pesticides from Golf Links

Tohru Morioka* and Akihiro Tokai*

ABSTRACT: Equilibrium and non-equilibrium Basin-Wide Ecological Models (BAWEM) were applied to estimate the ambient concentration of simazine, diazinon and chlorothalonil which were employed in the turf maintenance. The doses derived from their calculated concentrations and from human consumption of drinking water were compared with their 1% of ADI(Acceptable Daily Intake) and VSD (Virtually Safe Dose) value. The results obtained are summarized as follows;

(1)The range of ambient concentration of these chemicals was 0.02 - 0.38 mg/m^3 in the case of one golf course in the watershed concerned. Their maximum monthly concentrations obtained by non-equilibrium non-steady state BAWEM were 1.5 to 3 times larger than their annual mean concentrations.

(2)Among the indicative agro-chemicals, chlorothalonilis estimated to present the highest risks from both the view points of chronic as well as carcinogenic effects. The life-time cancer risk stemming from chlorothalonil is over ten to the minus 6 order of magnitude through the year.

(3)The risk level of agro-chemicals would exceed what the inhabitants could accept, if more than 2 golf links were developed in the watershed concerned.

Key words: Quantitative risk assessment, Reservoir contamination, Golf links development, Herbicide, Pesticide

1. Recent Land Development in Reservior Watershed Area

Drinking-water supply authorities in Japan are facing the serious problems of source-water pollution caused by micro pollutants such as THMs, TCE and other industrial chemicals as well as agro-chemicals. The land use in reservoir watersheds, downstream of which river water is withdrawn for municipal water supply, is the issue where there is conflict among competitive activity sectors including developers of golf links, water-supply authorities, and citizen's groups for environmental conservation. The risk assessment of herbicides and pesticides used on golf links should play a significant role in policy-making about river-basin management.

The river basin, which was selected for this case study, is located 50km from central Tokyo as illustrated in Fig. 1. A multi-purpose reservoir was constructed in 1988 on this river. A resort town with a population of seventy-five thousand, joined the water-resources development project so as to gain a stable drinking-water supply, bearing the burden of 8,000 million yen for a water volume of $1.5m^3/sec$. The prefectural government which had implemented the construction works, has

* Osaka University, Department of Environmental Engineering

examined the preliminary plan for development and conservation of the reservoir watershed, but a final plan has not materialized. Recently, three proposals for golf-link development in this watershed were submitted to the development-appraisal agency.

2.Percieved Risk Stemming from Agro-chemicals

The topic of herbicides and pesticides in golf links came to public attention, stimulated by the news of the rapid development of new golf links last year.

Herbicides and pesticides have different types of impacts on environmental and human health. Among various toxicological impacts, here, chronic and carcinogenic effects to human health are focused on. They are invisible, intangible, cumulative, of low-probability, irreversible and dreadful. Especially, cancer risk is sometimes emotionally referred to by mass media, so that citizens become more sensitive to persistent pesticide residues in food and drinking water.

Quantitative risk assessment of agro-chemicals used on the turf of the golf links in Japan has not been performed. Though some agro-chemicals have been found to be carcinogenic, the extremely small number of deaths related to carcinogens (around one victim per one million population) has not been perceived as useful information for behavioral choice, value judgment, and never as a tradable element in decision-making under any conflict situation.

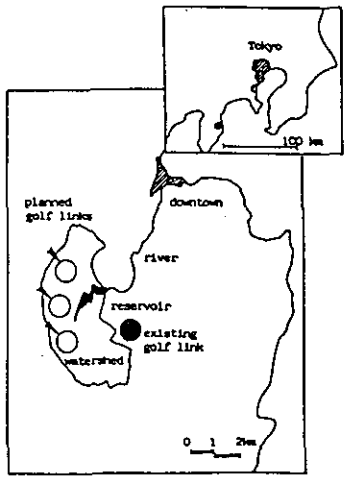


Fig. 1 Pilot study area

3. Fate and Exposure Route of Herbicides and Pesticides

Among many agro-chemicals, simazine, diazinon and chlorothalonil are selected as indicative chemicals for herbicides, insecticides and fungicides.

The major mechanisms accounting for the spreading or disappearance of agro-chemicals from the turf are the evaporation process to the air compartment, the degradation process in the soil compartment and the leaching process from the soil to the water compartment. The load of chemicals to the reservior is most influential in estimating concentrations. Though research on estimating the runoff rates of agro-chemicals are very limited(Maru 1985), a small part of the applied agro-chemicals are presumed to be transported into surface runoff water during the rainy season. The longer the persistency of chemicals in the reservoir, the higher the degree of possible human exposure to the chemicals. Mathematical fate models can be used to simulate the behavior of chemicals in the watershedand the reservoir. Scenarios concerning exposure through drinking water and the dose-response relationship based on the results of animal tests are usually followed by quantification of the estimated dosage

in the scenario. Finally, the ratios of estimated dosages to the ADI values in the drinking water and/or that to the VSD values are evaluated. We set up the following two scenarios. The first one, Case 1, is the case in which parameters related to chemical fate are expressed in terms of equilibrium partition coefficients and annually constant load to the environment. The second one, Case 2, is the case in which they are expressed kinetically and as a constant monthly load to the environment.

Two types of fate models are utilized to estimate the concentrations of agro-chemicals at the intake point for drinking-water supply. One is the equilibrium steady-state version of BAWEM(EBAWEM)(Morioka 1986, Morioka & Chikami 1986) predicting the annual average concentration of chemicals, in which the environment of the golf link is configured by using the average height of the atmospheric boundary sub-layer, the mean current velocity, and other topographical parameters. In this model, it is assumed that the partition equilibrium among each environmental media is attained. Another is the non-equilibrium non-steady-state BAWEM(NEBAWEM)(Morioka 1986, Morioka & Chikami 1986) forecasting the average monthly concentration of chemicals, which expresses both storm runoff from the land surface with rainfall as the driving force and persistency in the reservoir after sedimentation, biodegradation and volatilization.

Table 1 Estimated consumption amount of chemicals

ISO	Simazine	Diazinon	Chlorothalonil
Mean of monthly max. in operated for one golf links system	38.15 (kg/month)	7.16 (kg/month)	34.64 (kg/month)
Annual mean for one golf links system	76.3 (kg/year)	35.8 (kg/year)	173.2 (kg/year)

Table 2 Chemical properties of selected agro-chemicals widely used in golf links

ISO	Simazine	Diazinon	Chlorothalonil
IUPAC name	2-chloro-4,6-bis-(ethylamino-S-triazine)	O-(2-isopropyl-4-methyl-6-)O,O-diethylthiophosphate	tetrachloro isophthalonitrile
Mole. formula	$C_7H_{12}N_5Cl$	$C_{12}H_{21}O_3N_2PS$	$C_8N_2Cl_4$
Popular name	CAT	Diazinon	Daconil
Content(%)	50	4	70
MW	202	304	266
Henry's const.	1.3×10^{-8}(20℃)	3.0×10^{-7}(20℃)	3.0×10^{-9}(20℃)
Solubility(mg/l)	5	40	0.6
Pow*1	2800	76	24000
Koc*1	1801	251	5781
BCF	249	152	824
kd in soil(d)	84*2	31*4	101*6
kd in water(d)	30*3	11*5	36*7

*1Estimation from solubility (Kenaga E., 1979)
*2Pesticide fact sheet(U.S.EPA, 1984)
*3Pesticide fact sheet(U.S.EPA, 1984)
*4Estimation from kd in water
*5Jury, W. A.(1984)
*6Estimation from kd in water
*7Kanazawa, J.(1987)

The application amount of indicative chemicals was determined based on the results of a questionnaire survey promulgated by the Japan Greenkeepers Union as shown in Table 1. The properties of the selected chemicals as to environmental fate are summarized in Table 2.

The results of the model simulation are given in Table 3. Calculated concentrations of each chemical in all cases is in the range from ten to the minus two to minus one mg/m^3. The estimated values obtained by the two types of model simulation in Case 1 as shown in Table 3 are almost of the same order of magnituide for each ofthe chemicals. The maximum monthly concentrations of each agro-chemical obtained by using EBAWEM were about two times larger than their annual mean concentrations. Concentration of chlorothalonil is closest to the corresponding LC_{50} value among the three chemicals.

Table 3 Estimated concentration of chemicals in reservoir by using of EBAWEM and NEBAWEM

		EBAWEM($\mu g/l$)	NEBAWEM($\mu g/l$)
Case 1	simazine	0.275	0.155
	diazinon	0.116	0.023
	chlorothalonil	0.290	0.196
Case 2	simazine	-	0.378
	diazinon	-	0.062
	chlorothalonil	-	0.341

Case 1:Annual mean concentration of chemicals
Case 2:Manthly maximum concentration of chemicals

4. Toxicological Effects and Health Risk Evaluation

Toxicological effects are grouped into lethal/chronic effects and reversible/irreversible effects. Carcinogenicity is one of the important types of irreversible effects. The reversible effect is evaluated in terms of LC_{50}, NOAEL(Non-Observed Adverse Effect Level), LD_{50} and ADI. The VSD is used forcarcinogenic risk evaluation. In either of the two approaches to health risk evaluation, the probable dosage through drinking water was estimated by multiplying drinking-water volume by contaminant concentration.

The WHO's guidelines(WHO 1984) for drinking water recommends that a drinking-water volume of 2 liter/day/capita be used, and that an uncertainty factor in extrapolating the obtained NOAEL from animal tests to human, be divided by the inter-species sensitivity factor (10 from mouse/rat to human) and then redivided by the intra-species sensitivity factor(10 in the general case) for toxicants. In spite of further consideration of the contribution or assignment ratio through drinking water with respect to the total acceptable dose of toxicants, considering the worsening trend of agro-chemical contamination nowadays, the authors determined that the acceptable daily intake through drinking water is one percent of the ADI value.

The dosage level through which half of the test animals acquired

cancer, which is named as TD_{50}(Gold et al. 1984), was used for the estimation of human cancer risk. Assuming the reliability of the concept of the one hit-model, the following formula is obtained:

$$P(D) = 1 - \exp(-k \cdot D) \qquad (1)$$

Equation (1) yields the probability of human cancer developing from an extremely low dosage. Here, D and P(D) denote the dosage of chemicals and the probability of cancer (in the case of dosage of D), respectively. The guideline of the U.S. EPA recommends the assessor to adopt the 95% upper-bound estimation in the extrapolation from the raw dose-response data; however, this idea is not considered in this calculation. Table 4 shows the toxicological indices of these indicative chemicals.

The estimated risk level of agro-chemicals in the reservoir are presented in terms of the probable worse case and expected annual mean values as in Table 5. The maximum concentration in probable worse-case simulation shows toxicant concentration in the easily flushed condition under the monthly peak load of applied chemicals. The elimination and disappearance of toxicants in the purification process for drinking water was disregarded. The carcinogenic effects are estimated to be higher than the chronic effects for all chemicals examined. The carcinogenicity of chlorothalonil is estimated to be higher than the others, and the risk of chlorothalonil is in the order of 10^{-6} through the year.

The estimated dose of these chemicals is compared with the value of 1% of ADI. The ratios of estimated dosage to the 1% of ADI value vary in the

Table 4 Toxicological parameters of each chemicals

ISO	Simazine	Diazinon	Chlorothalonil
NOAEL(mg/kg/d)	7	0.2	0.3
ADI*1(mg/kg/d)	0.07	0.002	0.003
1% of ADI*2 (mg/kg/d)	0.0007	0.00002	0.00003
LC_{50}*3(mg/l)	>40(carp)	2.9(rainbow trout)	0.25(rainbow trout)
Mutagenicity*4	not available	negative	negative
TD_{50}(mg/kg/d)*5	260	6.23	2.01
VSD for 10^{-6} risk(mg/kg/d)*6	3.75×10^{-4}	9.00×10^{-6}	3.00×10^{-6}

*1 NOAEL, reported by small number of researchers, is devided by uncertainty factor 100.
*2 1% of ADI, acceptable daily intake through drinking water
*3 Nishiuchi(1984)
*4 *Ames test*, Shirasu(1982)
*5 U.S.NIH(1987)
*6 These values are determined by using of one hit model and value of TD_{50}.

range of 0.062-0.388 in the monthly-peak situation. On the contrary, in the case of the expected annual mean concentration, these ratios for 1% of ADI become rather lower, in the range of 0.023 - 0.196.

Table 5 Estimated risk levels of agro-chemicals

	Simazine	Diazinon	Chlorothalonil
High conc. in monthly max. (a) (μg/l)	0.378	0.062	0.341
Expected annual mean conc. (b) (μg/l)	0.158	0.023	0.196
Ratios for 1% of ADI (a)	0.018	0.104	0.378
(b)	0.0074	0.039	0.218
Ratios for VSD for (a)	0.034	0.334	3.79
10^{-6} life time cancer (b)	0.014	0.130	2.17

5. Conclusion

In this paper, quantitative risk assessment of herbicides and pesticides concerning golf links was performed. The chemical fate models, two types of BAWEMwere used for predicting concentrations in reservoir water. The estimated values range from 0.0023 mg/m^3 to 0.378 mg/m^3 for three selected agro-chemicals.

The risk level of humans exposed to these chemicals was calculated by using the concept of ADI for chronic effects and VSD for carcinogenic effects. Estimated values of the ratio of dosage to 1% of ADI range from 0.158 to 0.378 for simazine, 0.023 to 0.062 for diazinon and 0.196 to 0.341 for chlorothalonil in the case of monthly average forecasted concentration. The values of the ratios of dosage to VSD for ten to the minus six order lifetime risk ranged between 0.014 to 2.17 for expected annual mean concentration in reservoir water.

Judging from the estimated risk levels of these chemicals, the chronic and carcinogenic effects of chlorothalonil are dominant. Assuming three golf links were developed, it is expected that dosage through drinking water would exceed their ADI values. Accordingly, the risk level either for each or additive effects of the three agro-chemicals are judged beyond what is acceptable.

References

Gold, L. S., et al.(1984), A carcinogenic potency database of the standardized result of animal bioassays, Environmental Health Perspective, Vol.58, pp.9-319.

Maru, S.(1985), Monitoring of agro-chemicals in river water at Chiba prefecture, Seitai Kagaku, Vol.8, No.3, pp.3-9, (in Japanese)

Morioka, T.(1986), Approaches to environmental modelling of fate of chemicals in Japan, Proc. of Workshop of Environmental Modelling for Priority Setting among Existing Chemicals, GSF-Bericht, Ecomd press, pp.78-147.

Morioka, T. and Chikami, S.(1986), Basin-wide ecological fate model for management of chemical hazard, Ecological Modelling, Vol.31, pp.267-282.

WHO(1984), Guidelines for drinking water quality, Vol.2, Health criteria and other supporting information.

Comparative Risk Analysis and Environmental Priority Setting

Si Duk Lee and Lester D. Grant
U. S. Environmental Protection Agency
Office of Health and Environmental Assessment
Research Triangle Park, NC 27711

Although impressive progress has been made in successful environmental cleanup during the past two decades, there remain incrementally more difficult and more costly, complex environmental challenges. During the same period, environmental control technology has evolved from a single-medium approach to multimedia approaches to pollution prevention. Control programs of the past mainly focused on single compartments and, in some cases, contributed to moving pollutants from one medium to another. Unfinished Business, a project commissioned by former U.S Environmental Protection Agency (EPA) Administrator Lee Thomas, examined strategies for reducing major risks and recommended improved methodologies for assessing and comparing risks and risk reduction options. The report also pointed out that EPA's resource expenditures tended to be more closely aligned with public concerns and specific Congressional mandates with relatively low risk problems, such as hazardous waste sites, than with problems with potentially higher risk, such as indoor air pollution. In 1988 EPA Administrator William Reilly requested EPA's Science Advisory Board to evaluate the most serious hazards to human health and the environment and to refine the logical and scientific bases for EPA's priority setting. The evaluation resulted in Reducing Risk: Setting Priorities and Strategies for Environmental Protection. This report defined a set of fundamental principles for achieving broader, more integrated, and more carefully targeted environmental policies and presented important recommendations relative to setting priorities and strategies for environmental protection, an effort that involves comparison of a variety of risks to humans and to ecosystems. The need for improved priority setting, utilizing comparative risk analyses, is also gaining increased recognition internationally, as reflected in the development of risk comparison frameworks by The Netherlands and others.

Abstract of a presentation before the National Institute for Environmental Studies Workshop on Environmental Risk Assessment and Management for Toxic Chemicals, February 18 - 21, 1992, Tsukuba, Japan

OVERVIEW OF DISCUSSION

- Comparative Risk Analysis
  - best available tool for priority setting
- History
- Current Status
- Future

UNFINISHED BUSINESS: EPA's Assessment of Major Environmental Risks

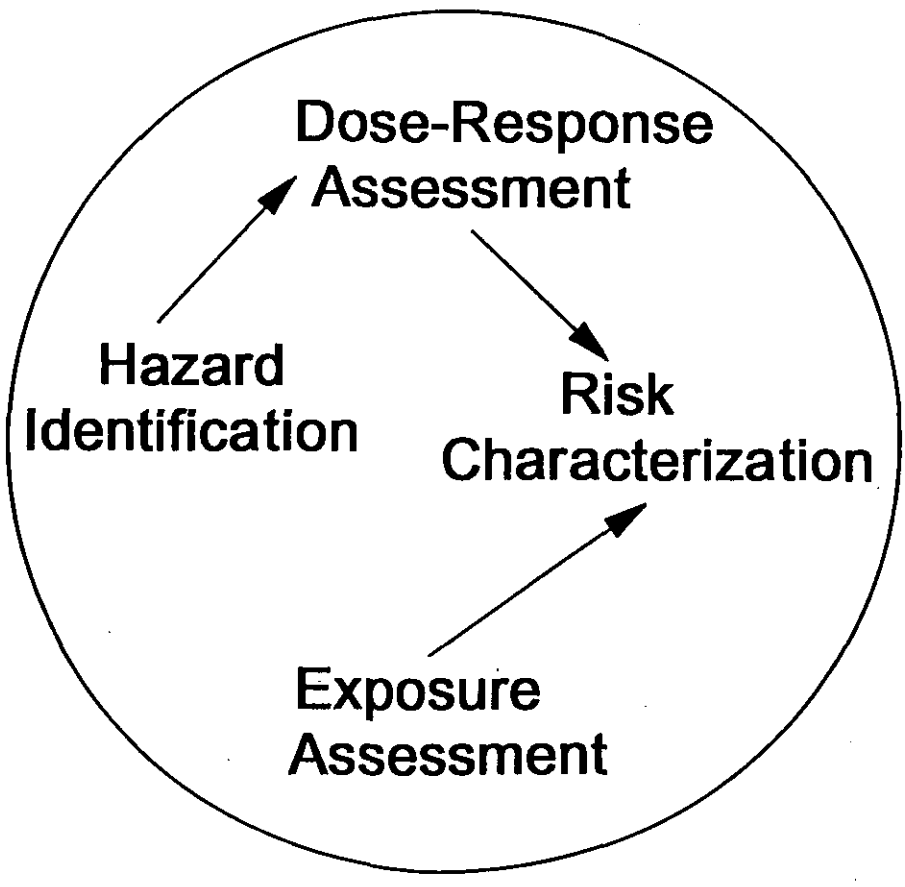
- Compared the risk associated with major environmental problems
- Results from this study and other relevant factors would be used in priority setting for EPA

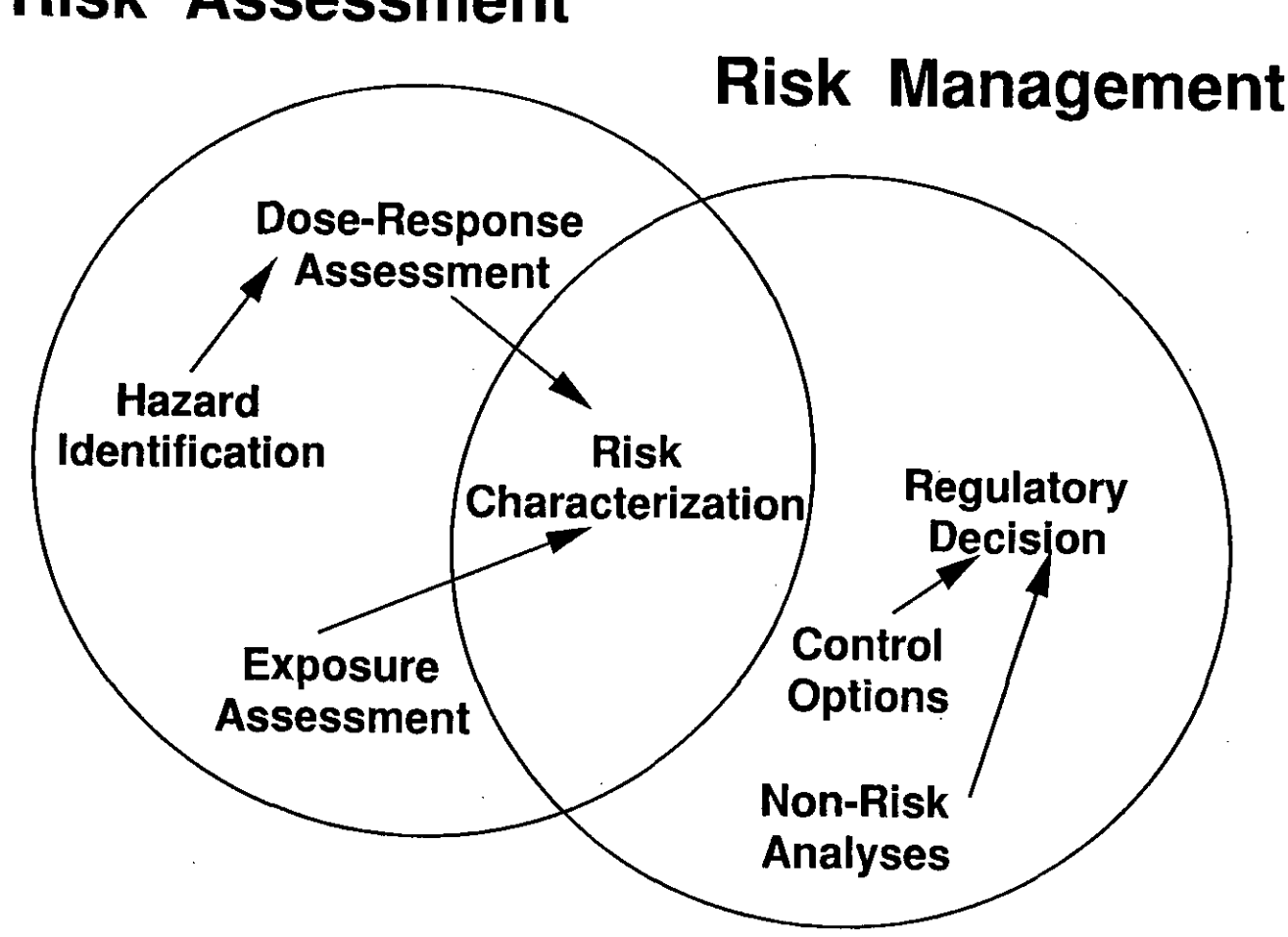
Why Comparative Risk Analysis

- Spent the last 20 years fixing the past 40 years of environmental mistakes
- Resources are not adequate to address all environmental problems equally
- Priorities need to be set for the most cost-effective risk management
- Many factors must be considered in priority setting, the relative risk of the problems to be addressed, is a point to start

---

Basic Model for Assessing Risk





COMPARATIVE RISK: A Priority Setting Tool

- Applying the basic risk assessment model to the problems to be address, allows one to establish varying level of risk for the problems that are to be addressed
- Can be applied to human health effects, ecological effects, and welfare impacts
- Process is a mechanism for determining relative risk, not absolute risk
- Currently the only tool available
- In many cases, sizable data gaps are still present
- No universally accepted methodology is available for comparing different kinds of risks

COMPARATIVE RISK: History

- 1987, assessment of the environmental risks EPA attempted to address:

  Human Health
  Ecological
  Welfare

- 1991, Science Advisory Board review and update

  Confirmed concept for assessing risk

- Planning for FY 1993, moving resources within the context of relative risk

  Change in Agency culture

COMPARATIVE RISK ANALYSIS: Current Status

- Progress has been slow
  Limited application to date

- Agency focus has been on the past
  Regulatory function
  Media specific (air, water, waste, etc.)

- Continued discussion on data limitations
  Best available for planning and priority setting

- Changing agency culture - setting priorities

COMPARATIVE ANALYSIS:
The beginning of the process

- Doing the analysis is not the end of the process but the beginning
- The greatest risk may not be where the resource are currently focused
  -- Public Perception
- The payoff is in making the necessary risk management decisions
- Cost per unit of risk reduced is an important component of the decision making process

---

RISK MANAGEMENT DECISIONS

- RANKING ENVIRONMENTAL PROBLEMS IS THE START
- COMPARATIVE RISK ANALYSIS CAN BE USED FOR:

  SETTING GEOGRAPHIC PRIORITIES WITHIN A SPECIFIC ENVIRONMENTAL PROBLEM

  IDENTIFYING PRIORITIES FOR STRATEGIES FOR ADDRESSING SPECIFIC ENVIRONMENTAL PROBLEMS

- COST EFFECTIVENESS IS STILL A CRITICAL DECISION TOOL

OBSTACLES IN USING RISK FOR PRIORITY SETTING

- Availability of data
- Uncertainty related to all aspects of data
- For EPA, legislative and regulatory responsibility
- Public perception* of risk versus technical assessment

HIGH

Hazardous Waste

Chemical Plant Accidents

Oil Spills

Indoor Air

Global Warming

LOW

* Roper poll, 1987

Role of Comparative Risk and Air Priorities

- Among the numerous air environmental problems, the approach can identify the most significant risks
- The risk management approach can set priorities for:
  - Research - Priorities for data collection
  - Program development
  - Program implementation
  - Targeting of sources, geographical assessment

Environmental Protection At The Crossroads