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プログラム・アブストラクト集
Program & Abstracts

第7回
内分泌攪乱化学物質問題に関する
国際シンポジウム

International Symposium on Environmental Endocrine Disrupters 2004

2004年12月15日(水)～17日(金)
名古屋国際会議場

Wednesday, December 15 - Friday, December 17, 2004
Nagoya Congress Center, Aichi, Japan

主　催：環 境 省
後　援：愛知県・愛知県教育委員会・名古屋市
協　力：日本内分泌攪乱化学物質学会

Organized by: Ministry of the Environment, Government of Japan
Supported by: Aichi Prefecture, Aichi Prefectural Board of Education, City of Nagoya
Cooperated by: Japan Society of Endocrine Disrupter Research

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ご挨拶

内分泌攪乱化学物質は、将来にわたって人の健康や生態系への影響が懸念される一方、科学的に未解明な点が多く残されています。環境省では内分泌攪乱作用が疑われている化学物質について、環境中の濃度測定や有害性の評価などを行いながら、諸外国や国際機関等との情報交換を進めてまいりました。

この一環として、平成10年度から毎年「内分泌攪乱化学物質問題に関する国際シンポジウム」を開催しています。世界各国から第一線で活躍中の研究者の御参加を得て、質の高い議論が活発に展開されてまいりました。その結果、シンポジウムに対して国内外から高い評価をいただいています。

シンポジウムの主なねらいは、

・我が国をはじめとする、世界各国の内分泌攪乱化学物質問題への取組状況について、情報を共有すること

・国際的な連携・協調により進めている内分泌攪乱化学物質問題の研究の方向性について議論すること

・身近な問題であると同時に、地球規模の問題でもある化学物質への対応について、各方面の関係者による多面的な意見交換を行うこと

の３点です。

今年度は、内分泌攪乱化学物質問題についての正確な情報を今後更に広く国民に伝えるため、環境教育をテーマとしたパネルディスカッションを行います。また、リスクコミュニケーションに着目したセッションを予定しています。さらに、内分泌攪乱化学物質問題に関するこれまでの環境省の取組を紹介させていただくほか、北里大学の養老孟司教授による特別講演を予定しています。

この国際シンポジウムが、世界各国の研究者はもとより、国民にとって意義のある会議となることを希望しています。是非とも多くの方々が御参加くださるようお願い申し上げます。

2004年９月

環境大臣　小池百合子

Greetings

To the distinguished participants of the International Symposium on Environmental Endocrine Disrupters,

Endocrine disrupters, also known as EDs, have become a topic of great concern among the general public because of their adverse effects on human beings and wildlife. And still now, so much remains to be explored scientifically. The Ministry of the Environment of Japan is therefore conducting the measurement of concentrations in the environment and hazard assessment of chemicals suspected of having endocrine disrupting effects, as well as engaging in exchanges of information with other countries and international organizations.

As part of these activities, the Ministry has been holding International Symposiums on Environmental Endocrine Disrupters since 1998. Past symposiums have brought together leading scientists from around the world and fostered productive discussions, with the result that the Symposium is highly valued internationally.

The Symposium has three major aims, namely, to share information on the initiatives being taken by various countries of the world in dealing with ED-related issues; to discuss the direction of future research on EDs through international cooperation; and to exchange wide-ranging opinions on chemicals in the environment as an issue of both local and global significance.

This year's symposium will have a panel discussion with the theme of environmental education and a session focusing on risk communication to provide more accurate information on the ED problem to the nation. In addition, the past efforts of the Ministry on the ED-related issues will be reviewed, and a special lecture by Professor Takeshi Yoro of Kitazato University will also be provided.

This symposium represents a significant opportunity for scientists and the general public from countries around the world to learn from and share with each other, and I look forward to its meaningful results yet again this year.

September 2004

小池百合子

KOIKE Yuriko

Minister of the Environment, Japan

第7回 内分泌攪乱化学物質問題に関する国際シンポジウム

International Symposium on Environmental Endocrine Disrupters 2004

Program Open to the Public
一般向けプログラム

This program will be in Japanese only.

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2004年12月15日（水）　［一般向けプログラム］

13:30	**開会挨拶** 主催者挨拶　環境大臣　　小池　百合子 後援者挨拶　愛知県知事　　神田　真秋
13:40	**特別講演** ホルモンのはたらき 　婁老　孟司（北里大学）
14:40	**取組の現状** 　上家　和子（環境省） 　井口　泰泉（自然科学研究機構・岡崎統合バイオサイエンスセンター） 　岩本　晃明（聖マリアンナ医科大学） 　福島　健彦（環境省）
15:40	休　　憩
16:00- 18:00	**パネルディスカッション「環境ホルモン問題をどう伝えていきますか」** 　司　会：　室山　哲也（NHK解説委員） 　パネリスト：青山　博昭（財団法人残留農薬研究所） 　奥野　泰由（住友化学株式会社　生物環境科学研究所） 　上家　和子（環境省） 　牧　　宏（名古屋市立庄内小学校） 　婁老　孟司（北里大学）

講演者一覧

養老　孟司

北里大学 教授

1937年（昭和12年）神奈川県鎌倉市に生まれる。1962年（昭和37年）東京大学医学部卒業。一年のインターンを経て、解剖学教室に入る。以降解剖学を専攻。1967年（昭和42年）医学博士号習得。1981年（昭和56年）東京大学医学部教授に就任。東京大学総合資料館長、東京大学出版会理事長を兼任。1995年（平成7年）東京大学を退官。1996年（平成8年）北里大学教授に就任（大学院医療人間科学）。大正大学客員教授を兼任（人間学原論）。1998年（平成10年）東京大学名誉教授。1989年（平成元年）『からだの見方』（筑摩書房）でサントリー学芸賞を受賞。2003年（平成15年）『バカの壁』（新潮社）で毎日出版文化賞を受賞。主な著書：『養老孟司　ガクモンの壁』（日本経済新聞社）。『運のつき　死からはじめる逆向き人生論』（マガジンハウス）。ほか多数。

上家　和子

環境省 環境保健部 環境安全課長

1982年（昭和57年）広島大学医学部卒業。厚生省児童家庭局母子衛生課、環境庁企画調整局環境保健部保健業務課、埼玉県衛生部医療整備課長、労働省労働基準局安全衛生部労働衛生課主任中央じん肺診査医、厚生労働省関西空港検疫所長、環境省環境保健部企画課特殊疾病対策室長等を経て、2004年（平成16年）4月　環境省総合環境政策局環境保健部環境安全課長。

井口　泰泉

自然科学研究機構・岡崎統合バイオサイエンスセンター 教授

岡山大学大学院修士課程修了、東京大学理学博士、1979年（昭和54年）に横浜市立大学文理学部助手、1981-83年（昭和56-58年）カリフォルニア大学バークレー博士研究員、横浜市立大学助教授を経て1992年（平成4年）教授、2000年（平成12年）からは基礎生物学研究所教授を経て、自然科学研究機構・岡崎統合バイオサイエンスセンター教授に就任して、現在に至る。マウス、魚やカエルを用いてホルモンや内分泌かく乱物質の発生影響を研究している。著書に「細胞を中心とした生物学」（広川書店）、『器官形成』（培風館）、『生殖異変』（かもがわ出版）、『環境ホルモンを考える』（岩波書店）、この他アメリカでの著書、学術論文多数。日本内分泌攪乱化学物質学会副会長、環境省、厚生労働省などの委員。

岩本　晃明

聖マリアンナ医科大学 泌尿器科・生殖医療センター 教授

1970年（昭和45年）横浜市立大学医学部卒業。医学博士。1986年（昭和61年）客員教授としてカナダケベック州マックギル大学医学部へ男性不妊症の研究のため留学。帰国後1989年（平成元年）より聖マリアンナ医科大学医学部泌尿器科助教授、1996年（平成8年）より、同教授、現在に至る。専門は泌尿器科・アンドロロジー・生殖医学。造精機能障害の臨床的・基礎的研究に従事し、1997年（平成9年）よりコペンハーゲン大学スカケベック教授との国際共同研究で環境ホルモンの男性生殖機能への影響について疫学調査に参加している。

福島　健彦

環境省 環境保健部 環境安全課 課長補佐

1990年（平成2年）3月、京都大学理学部卒業。環境庁環境保健部保健調査室、国立環境研究所、経済産業省産業技術環境局研究開発課等を経て、2001年（平成13年）9月より環境省環境保健部環境安全課。本年2～7月、人事院短期在外研究員として米国環境保護庁（EPA）に派遣。

室山　哲也

NHK解説委員

1976年（昭和51年）NHK入局。「ウルトラアイ」「クローズアップ」などの科学番組ディレクターの後、チーフプロデューサーとして「NHKスペシャル」や「クローズアップ現代」を担当。特に脳科学（「多重人格」「ザ・ブレイン」（10本シリーズ）「驚異の小宇宙人体2～脳と心」（6本シリーズ）「脳死」）科学技術（「チェルノブイリ原発事故」「残留化学兵器」「原爆」他）環境問題（「北極圏」他）災害（「阪神大震災」他）を重点テーマに制作。NHKエンタープライズ21時代は、イベント（ロボコン他）や大型映像、博物館をプロデュース。衛星ハイビジョン局でカルチャー番組全体統括チーフプロデューサー。現在解説委員。科学技術、生命・脳科学、環境、宇宙工学などを中心に論説を行っている。モンテカルロ国際映像祭金賞受賞・放送文化基金賞、上海国際映像祭撮影賞・科学技術映像祭科学技術長官賞、橋田壽賀子賞ほか受賞。

青山　博昭

財団法人残留農薬研究所 毒性部 副部長 兼 生殖毒性研究室 室長

1978年（昭和53年）名古屋大学農学部畜産学科卒業（家畜育種学専攻）、農学博士（名古屋大学大学院農学研究科）。大学卒業後、財団法人残留農薬研究所において、農薬等の化学物質あるいは遺伝子突然変異に起因する生殖発生異常に関する研究に従事。現在、同研究所毒性部副部長兼生殖毒性研究室長。この間、1994年（平成6年）に日本先天異常学会奨励賞を受賞。1994年（平成6年）から1997年（平成9年）まで、米国国立環境保健科学研究所（NIEHS）留学。

奥野　泰由

住友化学株式会社 生物環境科学研究所 主席研究員

1974年（昭和49年）大阪府立大学大学院農学研究科修士課程終了（獣医学専攻）。同年、住友化学工業株式会社に入社、各種化学物質の安全性研究に従事。1998年（平成10年）グループマネージャー。1989年（昭和63年）農学博士取得。日本トキシコロジー学会等評議員。朝倉書店『トキシコロジー』・中山書店『最新薬性病理学』執筆（共著）。

牧　宏

名古屋市立庄内小学校 教諭

1968年（昭和43年）愛知教育大学教育学部卒業。1968年（昭和43年）～現在　名古屋市立公立小学校勤務。あいち環境教育フォーラム実行委員（愛知県主催2001年（平成13年））、あいちエコカレッジネット運営委員（愛知県主催2002・2003年（平成14・15年））。全国小中学校環境教育賞受賞（5・8・10回日本児童教育振興財団主催）、環境教育コンクール特別賞受賞（自然・文化創造会議主催2002年（平成14年））、学校の特色に応じた総合的な学習の研究と実践論文入選（日動火災教育振興財団主催）。今回パネルディスカッションのためのモデル授業を実施。

第7回 内分泌攪乱化学物質問題に関する国際シンポジウム

International Symposium on Environmental Endocrine Disrupters 2004

Program for Experts
専門家向けプログラム

セッション1～6の全てに同時通訳があります。
Interpretation will be available in Session 1-6.

2004年12月15日（水）～17日（金） 名古屋国際会議場

Wednesday, December 15 - Friday, December 17, 2004
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Thursday, December 16, 2004 (Program for Experts)

9:00-11:30 — **Session 1 Basic Science** P. 24

Chairpersons: Yoshitaka Nagahama (National Institute for Basic Biology, National Institute of Natural Sciences, Japan)
Jun-ichi Nishikawa (Osaka University, Japan)

Effects of Suspected Endocrine Disruptors on Nuclear Receptor Family
Jun-ichi Nishikawa (Osaka University, Japan)

Roles of AhR in Endocrine Disruptive Effects by Polycyclic Aromatic Hydrocarbons
Yoshiaki Fujii-Kuriyama (University of Tsukuba, Japan)

Thyroid Hormone, Brain Development, and the Environment
R.Thomas Zoeller (University of Massachusetts-Amherst, USA)

Estrogenic Disruption of the Male Urogenital System
Barry G. Timms (University of South Dakota, USA)

Expression Profiling EDC Actions in the Brains of Aquatic Vertebrates: Approaches and Challenges
Vance Trudeau (University of Ottawa, Canada)

11:30 — Lunch

13:00-16:00 — **Session 2 Wildlife** P. 29

Chairpersons: Taisen Iguchi (Okazaki Institute for Integrative Bioscience, National Institute of Natural Sciences, Japan)
Satoshi Hagino (Sumika Technoservice Corporation, Japan)

Endocrine Disruption in a Small Cladoceran Crustacean
Norihisa Tatarazako (National Institute for Environmental Studies, Japan)

Effects of Low Bisphenol A Concentrations in Prosobranch Mollusks
Jörg Oehlmann (Johann Wolfgang Goethe University Frankfurt am Main, Germany)

Oestrogen and Androgen Receptor Agonists: Identification and Measurement of *in vitro* Activity in the Aquatic Environment
Kevin V. Thomas (CEFAS, UK)

Evidence Derived from Field Surveys that Indicates Estrogenic Endocrine Disruption is Widespread in the Marine Environment
Alexander P. Scott (CEFAS, UK)

Organotin Compounds are Potent Inducers of Adipogenesis in Vertebrates
Bruce Blumberg (University of California, Irvine, USA)

Noises of Genetic Variation in Estimating Effects of Environmental Factors in Animals: A Review
Takao Namikawa (Nagoya University, Japan)

16:00 — Break

16:30-19:00 — **Session 3 Exposure** P. 35

Chairpersons: Shinsuke Tanabe (Ehime University, Japan)
Jun Sekizawa (University of Tokushima, Japan)

Phenolic Endocrine Disrupting Chemicals (Alkylphenols and Bisphenol A) in Asian Waters
Hideshige Takada (Tokyo University of Agriculture and Technology, Japan)

Human and Wildlife Exposures to Persistent Brominated Flame Retardants
Åake Bergman (Stockholm University, Sweden)

PCB Metabolites in Humans with Focus on OH-PCBs and $MeSO_2$-PCBs
Åake Bergman (Stockholm University, Sweden)

Rating Risks of Chemical Exposures: Dose and Time
Robert I. Krieger (University of California, Riverside, USA)

Multi-Component Mixtures of Endocrine Active Chemicals - Experimental Requirements and Recent Test Results
Andreas Kortenkamp (University of London, UK)

Friday, December 17, 2004 (Program for Experts)

9:00-11:10

Session 4 Human Health

P. 40

Chairpersons: Chisato Mori (Chiba University, Japan)
Tsunehisa Makino (Tokai University, Japan)

Commentator: Richard A. Becker (American Chemistry Council, USA)

Dioxin Health Effects on Humans Twentyeight Years after the "Seveso" Accident
Paolo Mocarelli (University of Milano-Bicocca, Italy)

Longitudinal Studies of Children's Health
Ellen K. Silbergeld (Johns Hopkins Bloomberg School of Public Health, USA)

Biomonitoring: An Integral Part of Exposure Analysis
Larry L. Needham (CDC, USA)

DNA Methylation Profiles for Evaluation of Epigenetic Risk
Kunio Shiota (The University of Tokyo, Japan)

11:10 Lunch

12:30-14:30

Session 5 Future Research Directions

P. 44

Chairpersons: Junzo Yonemoto (National Institute for Environmental Studies, Japan)
Mineo Yasuda (Hiroshima International University, Japan)

Evaluation of Chemicals for Endocrine Disruption: Future Research Needs
Richard E. Peterson (University of Wisconsin, USA)

Effects of Endocrine Disruptors on Behavioral Developments of the Brain and Neurodevelopmental Disorders—PCBs and Some Agricultural Chemicals Disrupt Gene Expressions, Suggesting a Causal Factor of LD, ADHD and Autism
Yo-Ichiro Kuroda (Tokyo Metropolitan Institute for Neuroscience / CREST, Japan)

Ecotoxicogenomics & the Assessment of Endocrine Disrupters in Aquatic Organisms: Future Opportunities and Validation Needs
Thomas H. Hutchinson (AstraZeneca R&D, Sweden)

Further Viewpoints of Epidemiological Studies for Detecting Subtle Effects in Children Exposed to Endocrine Disrupting Chemicals during Gestational Periods
Reiko Kishi (Hokkaido University, Japan)

14:30 Break

This session will be held in Japanese and interpreted into English.

15:00-17:30

Session 6 Risk Communication

P. 48

Chairpersons:
Junko Nakanishi (National Institute of Advanced Industrial Science and Technology, Japan)
Iwao Uchiyama (Kyoto University, Japan)

Effective Risk Communication: Its Philosophy and Technique
Tomio Kinoshita(Koshien University, Japan)

Risk Perception of Endocrine Disrupting Chemicals
Toshiko Kikkawa (Keio University, Japan)

What and Why We Lay Persons Don't Understand, and How You Experts Misjudge Them
Hiroo Yamagata (Reviewer, Translator, Japan)

このセッションは日本語で行われます。

セッション 6　リスクコミュニケーション

P. 48

座　長：
中西　準子（産業技術総合研究所）
内山　巌雄（京都大学）

リスクコミュニケーションの思想と技術
木下　冨雄（甲子園大学）

内分泌攪乱化学物質に対するリスク認知
吉川　肇子（慶應義塾大学）

一般人の誤解と専門家のかんちがい：現境問題の何がなぜわかりにくいのか
山形　浩生（評論家・翻訳家）

Session 6

Risk Communication of Endocrine Disrupting Chemicals Produced by Industries Among Consumers, Producers, Administrators and Scientists

Saburo Matsui (Kyoto University, Japan)

Takashi Higaki (Journalist, Writer, Japan)

セッション6

消費者、製造業者、行政、科学者の間で、産業によって製造された内分泌撹乱物質のリスクコミュニケーション

松井　三郎（京都大学）

環境リスクとジャーナリズムの問題点

日垣　　隆（ジャーナリスト・作家）

第7回 内分泌攪乱化学物質問題に関する国際シンポジウム

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講演者一覧

List of Speakers

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List of Speakers

Yoshitaka Nagahama

Professor and Vice-Director, National Institute for Basic Biology, National Institute of Natural Sciences, Japan

1971 Ph.D. Hokkaido University. 1972-74 Postdoctoral Fellow, Department of Zoology, University of California, Berkeley. 1974-76 Postdoctoral Fellow, Department of Zoology, University of British Columbia, Vancouver, Canada. 1977 Research Assistant, Department of Zoology, University of California, Berkeley. 1977-86 Associate Professor, National Institute for Basic Biology. 1986- Professor. 2004- Vice-Director National Institute for Basic Biology. 2001- Vice-President International Federation of Comparative Endocrinological Societies. 1987 The Fisheries Prize, 1988 The *Grace Pickford Medal (International* Federation of Comparative Endocrinological Societies), 1989 Inoue Science Award, 1989 The Zoological Society Prize.

Jun-ichi Nishikawa

Associate Professor, Environmental Biochemistry, Graduate School of Pharmaceutical Sciences, Osaka University, Japan

Graduated from the Faculty of Engineering Sciences, Osaka University in 1982 and received Ph.D. from the Faculty of Pharmaceutical Sciences, Osaka University in 1987. He worked as a research associate in Sumitomo Chemical Co., Ltd. from 1987 to 1989, and moved to Osaka University in 1989. His main research fields are transcriptional regulation of nuclear receptors and molecular mechanism of action by endocrine disruptors.

Yoshiaki Fujii-Kuriyama

Professor, Basic Medicine, Center for Tsukuba Advanced Research Alliance, University of Tsukuba, Japan

<Education> 1959-1963: Faculty of Science, University of Tokyo, 1963-1965: Department of Biochemistry, Graduate School of Science, University of Tokyo <Research and professional experience> April 1965 - February 1975: Researcher, Central Research Laboratories, SANKYO Co., LTD. March 1975 - August 1977: *Instructor, Kanazi Medical University*, September 1977 - August 1978: Member, Japanese Foundation for Cancer Research. September 1978 - March 2001: Professor, Graduate School of Science, Tohoku University. April 2001 - present: Professor, Graduate School of Life Science, Tohoku University. Visiting professor, Center for TARA, University of Tsukuba. <Membership of learned societies> Japanese Biochemical Society, Japanese Cancer Society and The Molecular Biology Society of Japan.

R. Thomas Zoeller

Professor and Chair, Biology Department, University of Massachusetts-Amherst, Laboratory of Molecular and Cellular Neurobiology, USA

Dr. Zoeller obtained his B.S. in Biology from Indiana University, and his Ph.D. in endocrinology from Oregon State University. He then took a postdoctoral position in the Laboratory of Cell Biology at the National Institute of Mental Health followed by a staff position in the Laboratory of Neurochemistry at the National Institute of Neurological Disorders and Stroke. He then joined the medical faculty at the University of Missouri School of Medicine and most recently joined the faculty at the University of Massachusetts-Amherst. Dr. Zoeller was a standing member of the US EPA's Endocrine Disruptor Screening and Testing Workgroup.

Barry G. Timms

Professor, Division of Basic Biomedical Sciences, School of Medicine, University of South Dakota, USA

Dr. Timms is a reproductive biologist with a Master's degree from Aston University and *Ph.D. in Biological Sciences from the Tenovus* Institute for Cancer Research, University of Wales College of Medicine, UK. Following postdoctoral studies at the University of Iowa, he joined the Basic Science Faculty at the University of South Dakota School of Medicine (USDSM) in 1985. His studies over the past 25 years have focused on the biology of the prostate with an emphasis on structure and function. More recently this research has been directed towards understanding the cellular mechanisms associated with endocrine disruption of the male urogenital system and the effects of fetal exposure to environmental estrogens on the growth of the prostate at critical periods of organ development. Dr. Timms has served as an Executive Committee member of the Society for Basic Urological Research.

Vance Trudeau

Associate Professor, Department of Biology, Centre for Advanced Research in Environmental Genomics, University of Ottawa, Canada

Vance is interested in how sex steroids affect gene expression in the brain. In particular his lab has studied the effects of estrogens and estrogenic EDCs in fish, tadpoles and turtles. His lab is developing a microarray for the goldfish brain to asess the effects of EDCs. Development of in vitro and in vivo reporter gene assays to assess the effects of estrogens and peroxisome proliferators is curently underway. Please consult www.teamendo.ca/community for other *research projects.*

Taisen Iguchi

Professor, Okazaki Institute for Integrative Bioscience, National Institute of Natural Sciences, Japan

Received his Master of Science at Graduate School of Science, Okayama University and Doctor of Science, University of Tokyo. Dr. Iguchi joined the Faculty of Humanities and Sciences at Yokohama City University as a research assistant in 1979. He became an associate professor, and was later promoted to a professor in 1992. During these years, he conducted research first as a postdoctoral researcher and then as a visiting researcher at the University of California, Berkeley. In 2000, he was appointed professor at the National Institute for Basic Biology at the Okazaki National Research Institute, and later at the Center for Integrative Bioscience of the same institute. From 1974, Dr. Iguchi conducted research at the laboratory of Dr. Noboru Takasugi, *President of Yokohama City University. He found that the exposure of* sex hormones and hormone-related agents into fetal and perinatal mice caused morphological disorders of the reproductive organs and accessory organs. He also found that female hormones are important in the masculinization of animals via the hypothalamus, which controls hormone secretion of gonads, and further found that hormones and hormone-related agents cause disorders in the bones and muscles of perinatal mice. Ideas arising from this research have been applied to fish and amphibians. Dr. Iguchi is currently planning work on the permeation of hormone-related agents into the placenta and the influence of hormone-related agents on gene functioning. As a leading scientist in this field, he has been invited in a number of international conferences. Dr. Iguchi is vice-president of the Japan Society of Endocrine Disrupter Research, and is a member of a number of councils within governmental organizations, including the Environment Agency Ministry of Labor, and Science and Technology Agency. Dr. Iguchi's recent publications include: *"Organogensis"; "The Toxicity o Hormones in Perinatal Life"(English); "Cell-centered Biology" "Tamoxifen Beyond the Antiestrogen"(English); "Reproduction Disaster"; and "Altering Eden: The Feminization of Nature."*

Satoshi Hagino

Manager, Environmental Health Science Center, Environmental Toxicology Group, Sumika Technoservice Corporation, Japan

1979 Completed the master course of the Faculty of Fisheries of Nagasaki University and joined Sumitomo Chemical Co., Ltd. Majoring in ecotoxicology of agricultural chemicals using many kinds of aquatic and terrestrial organisms. 1993 Senior research associate, Environmental Health Science Laboratory. 1992 Joined Sumika Technoservice Corporation to establish new businesses for environmental technology. 2002 Manager, Environmental Toxicology Group.

Norihisa Tatarazako

Senior Researcher, Ecological Chemistry Section, Environmental Chemistry Division / Endocrine Disrupter Research Laboratory, National Institute for Environmental Studies, Japan

1986 Graduated from the Department of Forestry, Faculty of Agriculture, the University of Tokyo. 1988 Completed a Master's degree from the Graduate School of Agricultural Sciences, the University of Tokyo. 2002 Doctor of Agriculture at the University of Tokyo. 1988-2001 Employed at Oji Paper Co., Ltd. 2001- Employed at the Environmental Chemistry Division, National Institute for Environmental Studies as the Senior Researcher of the Ecological Chemistry Section. Specialty: Endocrine disruptors, toxicity evaluation.

Jörg Oehlmann

Full Professor and Head of Department, Ecology and Evolution, Johann Wolfgang Goethe University Frankfurt am Main, Germany

<Personal backgrounds> October 1981 - December 1988: Study of Biology and German for "Lehramt für die Sekundarstufen II und I" at the WWU Münster. November 1990 - September 1994: Research Assistant at the Institute for Special Zoology and Comparative Embryology, Westfälische Wilhelms University (WWU) Münster. 28th January 1994 Graduation as Dr. rer. nat. at the WWU Münster. October 1994 - December 1998: Research Assistant at the International Graduate School Zittau (IHI Zittau). October 1994 - April 2001: Head of the working group "Human- and Ecotoxicology" at the Environmental Technology Department Teaching in Ecology, Toxicology and Ecotoxicology. June 1996 - April 2001: Vice-Chairperson of the Department of Environmental Technology. 18th December 1998: Habilitation at the IHI Zittau. Venia legendi in "Ecology & Zoology". December 1998 - April 2001: Associate Professor (Privatdozent) at the IHI Zittau. Since May 2001: Professor for Ecology and Evolutionary Biology at the Johann Wolfgang Goethe University Frankfurt. Offered Chairs: 2003: University Landau, Environmental Sciences (denied in 2003). 2004: University Frankfurt, Aquatic Ecotoxicology (accepted 2004). <Main research topics and expertise> Endocrine disrupting chemicals: development of new test systems (especially with invertebrates), assessment strategies, hazard and risk assessment. Effects of pharmaceuticals on aquatic invertebrates. Sediment toxicology: development of new test systems and evaluation strategies. Biological effect monitoring in marine and freshwater environments, with special emphasis on metals, organometallic compounds and endocrine disrupting chemicals

Kevin V. Thomas

Topic Leader, Hazardous Substances Research, Centre for Environment, Fisheries and Aquaculture Science, UK

Dr Kevin V. Thomas is Topic Leader for Hazardous Substances Research at CEFAS, UK. He has been conducting research on the occurrence, fate and effects of hazardous substances for the past ten years. He is author of over fifty papers with a large number focusing on the identification of environmental contaminants through the use of bioassay directed fractionation techniques. He advises the UK, OSPAR and ICES on matters relating to hazardous substances in the marine environment.

Alexander P. Scott

Senior principal research scientist, Weymouth Laboratory, Centre for Environment, Fisheries and Aquaculture Science, UK

He is a holder of Individual Merit Promotion for research, has a DSc from St Andrews University and is an adjunct Professor at the Fisheries and Wildlife Department of Michigan State University. He has 30+ years experience in the field of fish reproduction - especially in relation to the endocrine control of annual reproductive cycles, the roles of steroids as both hormones and pheromones, and the impact of estrogenic endocrine disruption in marine fish.

Bruce Blumberg

Associate Professor, Department of Developmental and Cell Biology and Biomedical Engineering, University of California, Irvine, USA

Ph.D. from UCLA, 1987 (Biology). Postdoctoral training at UMDNJ, Robert Wood Johnson Medical School (1987-1988, extracellular matrix) and the Department of Biological Chemistry in the UCLA Medical School (1988-1992, molecular embryology). Appointed as Staff Scientist, The Salk Institute, La Jolla, CA (1992-1998) focusing on the molecular endocrinology of orphan nuclear receptors and their role in embryonic development and adult physiology. Joined the faculty at the University of California, Irvine in 1998. Current research focuses on early embryonic pattern formation, xenobiotic metabolism, differential effects of xenobiotic exposure on laboratory model organisms compared with humans and functional genomic approaches to better understand these problems.

Takao Namikawa

Professor, Laboratory of Animal Genetics, Division of Applied Genetics and Physiology, Graduate School of Bioagricultural Sciences, Nagoya University, Japan

1968 B.Agr., 1970 M.Agr., 1973-74 JSPS-Researcher, 1975-76 Research Assistant, 1977-88 Assistant Professor, 1983 Ph.D., of Nagoya University. 1988-95 Associate Professor, 1995-98 Professor of Faculty of Agriculture, Nagoya University, and 1998 to the present. 1984 Award of Japanese Society of Animal Science with genetical study on the history of cattle in eastern Asia. He is presidents of Japanese Society of Animal Breeding and Genetics and the Society for Researches on Native Livestock, Japan. His major interests are population genetics or genetic variabilities in domestic and laboratory animals as well as its wild populations.

Shinsuke Tanabe

Professor, Center for Marine Environmental Studies, Ehime University, Japan

1975 Graduated from Ehime University, Graduate School of Agriculture. 1977 Assistant Professor, Faculty of Agriculture, Ehime University. 1985 Awarded Ph.D. from Nagoya University. 1987 Associate Professor, Faculty of Agriculture, Ehime University. 1995 Professor, Faculty of Agriculture, Ehime University. 1999 Professor, Center for Marine Environmental Studies, Ehime University. 1985 Okada Prize from The Oceanographical Society of Japan. 1999 Nissan Science Prize from Nissan Science Foundation. 2000 Citation Classic Awards in Japan from ISI Thomson Scientific. 2004 Academic Awards from The Japan Society for Environmental Chemistry and The Society of Environmental Science, Japan. His current research efforts are aimed at understanding global contamination of endocrine disrupters and their toxic effects to humans and wildlife.

Jun Sekizawa

Professor, Faculty of Integrated Arts and Sciences, University of Tokushima, Japan

<Professor> Environmental Chemistry <Education: Final status> D. Phil., University of Tokyo, March 1971 <Fields of Specialization> Risk Assessment and Risk Communication on Chemicals, the Environment and Foods <Academic Appointments and Professional Experience> Researcher, Tokyo Metropolitan Institute of Environmental Sciences, 1971-75, Research Associate, State University of New York, 1975-78, Chief, Central Research Institute, Ogawa and Co.Ltd. 1978-82, Chief, National Institute of Health Sciences, Japan, 1982-2003, Professor, University of Tokushima, 2003-04, Chair, Committee on Risk Communication, Food Safety Commission, The Cabinet Office 2003-04 <Professional and Honorary Societies> President of the Society for Risk Analysis, Japan 2004-Today, Has been Participating in the Risk Assessment Activities of the International Programme on Chemical Safety (IPCS) of the World Health Organizations (WHO), 1982-Today.

Hideshige Takada

Associate Professor, Department of Environmental Science and Natural Resources, Laboratory of Organic Geochemistry, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Japan

<Short Scientific Biography> B.Sc. in Science (Tokyo Metropolitan University) in 1982. M.Sc. in Science (Tokyo Metropolitan University) in 1984. Ph.D. in Science (Tokyo Metropolitan University) in 1989. Abroad Study (Woods Hole Oceanographic Institution, MA, U.S.A.) Sep.1990 - May 1991. Visiting for lectures in June 1991. IAEA (Monaco), University of Paris (France), EAWAG (Switzerland), Plymouth Marine Laboratory (UK), CSIC (Spain). Okada Prize of the Oceanographic Society of Japan in 1993. Hirose Prize of the Japanese Society on Water Environment in 1995. <Field of Specialization> Environmental Organic Geochemistry.

Åake Bergman

Chair, Department of environmental chemistry, Stockholm University, Sweden

Bergman is working with organic chemical synthesis and radiosynthesis of individual congeners of environmental pollutants, their metabolites and abiotically formed degradation products. He is devoting part of his research to describe persistency by new approach. Åake Bergman is engaged in research improving analytical methodology for environmental contaminants. Much of his time goes to human and wildlife exposure assessments of environmental contaminants and their metabolites. He has for long been associated with research on PCB metabolites, brominated flame retardants and endocrine disrupters.

Robert I. Krieger

Extension Toxicologist, Entomology, University of California, Riverside, USA

Bob Krieger is Extension Toxicologist, University of California, Riverside. He holds a B.S. in Chemistry from Pacific Lutheran University in 1967 and a Ph.D. from Cornell University in 1970. He has held academic appointments at U.C. Davis (1971-1980) and in the WOI Regional Veterinary Medical Education Program. At Riverside he specializes in residential and agricultural pesticide exposure assessment. He has taught toxicology at both the undergraduate and graduate levels and received awards including the Society of ToxicologyÅfs Education Award. His research concerns the fate and effects of pesticides, risk assessments, and risk communication. His group has published over 300 papers and abstracts.

Andreas Kortenkamp

Senior lecturer, Center for Toxicology, School of Pharmacy, University of London, UK

Andreas Kortenkamp read chemistry and philosophy at Muenster University, Germany and obtained his PhD at Bremen University, Germany, with a thesis on the mode of action of carcinogenic chromium compounds. He is a Senior lecturer at the School of Pharmacy, University of London. His current research interests are in the area of mixture effects of endocrine disrupting chemicals. He is the coordinator of the EU-funded European Cluster for Research on Endocrine Disruption, CREDO.

Chisato Mori

Professor, Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University, Japan

Doctor of Medicine (M.D.) from Asahikawa Medical College in 1984, Doctor of Medical Science (D.Med.Sc; Ph.D) from Kyoto University, Graduate School of Medicine in 1989. 1984-1992: Research Associate, Department of Anatomy, Faculty of Medicine, Kyoto University, Kyoto, Japan. 1990-1992: Visiting Associate, Gamete Biology Section, Laboratories of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina, U.S.A. 1992-2000: Associate Professor, Department of Anatomy and Developmental Biology, Faculty of Medicine, Kyoto University, Kyoto, Japan. 2000-2001: Professor, Department of Anatomy and Cell Biology, School of Medicine, Chiba University, Japan. 2001- present: Professor, Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University, Japan.

Tsunehisa Makino

Professor and Chairman Department of Obstetrics and Gynecology, Tokai University Hospital, School of Medicine, Tokai University, Japan

1964 M.D. Keio University, School of Medicine, Tokyo, Japan. 1964-65 Rotating Intern, Keio University Hospital. 1965 National Board of Medical Examination (Registered No. 187877). 1965-69 Clinical Research Fellow, Dept.of Obstetrics and Gynecology, Keio University, School of Medicine. 1969 Ph.D. Keio University, Tokyo, Japan. 1969-70 Postdoctoral Fellow, Dept of Obstetrics and Gynecology, Keio University, School of Medicine. 1970 Research Fellow, Dept.of Anatomy, Laboratory of Human Reproduction and Reproductive Biology, Harvard Medical School, U.S.A. 1971 Associate, Dept. of Obstetrics and Gynecology, Harvard Medical School. 1972 Assistant Professor, Dept. of Obstetrics and Gynecology, Harvard Medical School. 1973 Associate Professor, Dept. of Obstetrics and Gynecology, Tokyo Dental College. 1978 Assistant Professor, Dept. of Obstetrics and Gynecology, School of Medicine, Keio University. 1995- Professor and Chairman, Dept. of Obstetrics and Gynecology, School of Medicine, Tokai University. 2001- Director and Chairman, Department of Obstetric and Gynecology, Center for Growth and Reproductive Medicine, School of Medicine, Tokai University. 2003- Director, Center for Perinatology, School of Medicine, Tokai University <Awards> 1972 Prize Thesis, American Association of Obstetricians and Gynecologists. 1972 Harvard University, Milton Fund Award. 1974 Kitasato Award. 1980 Kato Award of Medical Physiology. 1983 Japan Medical Association Research Aid Grant Award.

Paolo Mocarelli

Full Professor of Clinical Biochemistry at the Medical School, University Milano-Bicocca, Italy

Director of the University Institute of Laboratory Medicine, Hospital of Desio - Milano, Italy. Coordinator of the Clinical Laboratory Projects for monitoring health of the population of the Seveso area, since the dioxin accidental pollution in 1976. WHO expert for the effects of dioxin on humans. Author of more than 180 papers. President (1995) of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology. (SIBioC). President, in 1999, of the "19th International Symposium on Halogenated Environmental Organic Pollutants" with the partecipation of more than 1000 experts.

Ellen K. Silbergeld

Professor, Environmental Health Sciences, Johns Hopkins School of Public Health, USA

Dr Ellen Silbergeld, Professor of Environmental Health Sciences (with joint appointments in Epidemiology and in Health Policy and Management) at the Johns Hopkins University Bloomberg School of Public Health, conducts research that connects environmental and occupational exposures to health risks in human populations. Her research has employed both experimental models and epidemiological studies to accomplish these goals. Her areas of current research include: understanding the environmental and human health impacts of antibiotic use in food animal production, understanding the mechanisms of mercury immunotoxicity, and the potential role of immunologic dysfunction in mercury-induced neurodevelopmental toxicity, decreased host resistance to infection, and increased risks of chronic disease, and health risks associated with endocrine disruption. She is also involved in epidemiological studies of the effects of toxic metals on cardiovascular function. Dr Silbergeld received her BA degree summa cum laude from Vassar College and a PhD from the Whiting School of Engineering at Johns Hopkins University, with postdoctoral training in environmental health sciences at the School of Public Health. Prior to her current academic position, she has held scientific positions at NIH, the Environmental Defense Fund, and the University of Maryland Medical School. She has been appointed to numerous consultant and expert advisory committees for the US EPA, CDC, National Research Council, and the NIH; also for WHO, ILO, OECD, the World Bank, UNEP, and UNDP. She has also served on many peer review panels for NIH, EPA, NIOSH, NSF, and foundations, including chairing the epidemiology panel for the Howard Hughes Medical Institute. She is editor in chief of Environmental Research. Dr Silbergeld's work has been recognized by fellowships and awards from the Fulbright Commission, the Rockefeller Foundation, the American Public Health Association, and a "genius" award from the MacArthur Foundation.

Larry L. Needham

Chief, Organic Analytical Toxicology Branch, Centers for Disease Control and Prevention, USA

His specialty is the development and application of analytical methods for measuring environmental chemicals in humans. Dr. Needham is author or co-author of more than 300 peer-reviewed publications and numerous book chapters. He is Past President of the International Society of Exposure Analysis, an editor of Chemosphere, and a long time-member of the International Advisory Board for the annual Dioxin meetings.

Kunio Shiota

Professor, Animal Resource Sciences and Veterinary Medical Sciences, The University of Tokyo, Japan

<Education> 1973: B.S. & D.V.M., Miyazaki University, Veterinary Medical Science, (Physiology). 1975 M.S., The University of Tokyo (Prof. Y. Suzuki) (Physiology). 1979 Ph.D. The University of Tokyo (Prof. Y. Suzuki) (Endocrinology). <Major Research Interest> "Epigenetics, Molecular Endocrinology & Cellular Biochemistry" During the development of mammals, most cells differentiate without changing the DNA sequence, while the differentiation of a given cell type is associated with activation of particular set of genes and inactivation of other sets. DNA methylation is associated with gene-silencing and changes in chromatin structure. Recently, we found a numerous number of tissue-dependently and differentially methylated regions (T-DMRs). T-DMRs are widespread in the mammalian genome and the methylation pattern is specific to the cell types, suggesting that the formation of DNA methylation pattern is one of the principal epigenetic events underling mammalian development. We are investigating the mechanism for DNA methylation pattern and its biological roles. <Professional Experience> 1977-1978, Postdoctoral fellow, "Washington University, Medical School" (Prof. W.G. Wiest). 1979-1987, Scientist, "Biology Research Laboratories, Central Research Division, Takada Chemical Industries, LTD". 1987-1989, Associate Professor, "The University of Tokyo, Laboratory of Veterinary Physiology". 1989-1998, Associate Professor, "The University of Tokyo", Laboratory of Cellular Biochemistry" "Visiting Researcher RIKEN Institute". 1998-present, Professor, "The University of Tokyo", Laboratory of Cellular Biochemistry". (1989-1999) Visiting Researcher of "RIKEN Institute". (2000-2001) Adjunct Professor of "University of Hawaii, Department of Anatomy and Reproductive Biology". (2003-Present) Visiting Professor of "National Institute of Genetics, Division of Applied Genetics".

Junzo Yonemoto

Leader, Health Effects Research Team, Endocrine Disruptor and Dioxin Research Project, National Institute for Environmental Studies, Japan

Graduated from Tokyo University in 1973 and obtained his Ph. D. (Health sciences) at Graduate School, Tokyo University in 1982. 1982-1984 Research Assistant, Faculty of Medicine, Tokyo University, 1984 to present National Institute for Environmental Studies, 2001 to present Leader, Health Effects Research Team, Endocrine Disruptor & Dioxin Research Project. <Research Field> Environmental Toxicology. Reproductive toxicology of dioxins and related compounds. A director of Japan Society of Endocrine Disrupters Research.

Mineo Yasuda

Professor, Department of Clinical Engineering, Faculty of Health Sciences, Hiroshima International University, Japan

1962 Graduated from Kyoto University, Faculty of Medicine. 1963-71 Instructor of Anatomy, Faculty of Medicine, Kyoto University. 1971-75 Assistant Professor of Anatomy, Kyoto Prefectural University of Medicine. 1972-74 Research Associate, Department of Medical Genetics, University of British Columbia, Canada. 1975-77 Head, Department of Perinatology, Institute for Developmental Research, Aichi Prefectural Colony. 1977-2001 Professor of Anatomy, Hiroshima University School of Medicine. 2001- Professor of Clinical Engineering, Faculty of Health Sciences, Hiroshima International University. Field of interest: Reproductive and developmental toxicology of chemicals including dioxin. 1998 Award for scientific achievement from the Society of Environmental Science of Japan: Mechanisms of abnormal development by dioxins.

Richard E. Peterson

Professor of Pharmaceutical Sciences, School of Pharmacy, Molecular and Environmental Toxicology Center, and Endocrine Disruption International Cooperative Research, University of Wisconsin, USA

Dr. Peterson is Professor and Executive Director of Endocrine Disruption International Cooperative Research (EDICOR) at the University of Wisconsin. He has more than 200 peer-reviewed publications in toxicology. He has trained 24 graduate students for the Ph.D. and 26 Ph.D.s have completed postdoctoral training in his laboratory. Dr. Peterson's research is focused on mechanisms of dioxin and PCB reproductive and developmental toxicity in laboratory rodent and fish species. He is the recipient of an NIH Research Career Development Award, Society of Toxicology Frank Blood Award, Kenneth P. DuBois Award, and NIH MERIT Award for his research in toxicology.

Yo-Ichiro Kuroda

Distinguished Researcher, Department of Molecular and Cellular Neurobiology, Tokyo Metropolitan Institute for Neuroscience / Principal Investigator, CREST, Japan

In 1943, born in Tokyo. 1966 Graduated University of Tokyo (Biochemistry), in 1971, Graduate School, University of Tokyo (Molecular Genetics). 1971-73, Department of Biochemistry, Institute of Psychiatry, University of London (Molecular mechanism of memory) as a British Council Scholar. 1973- Department of Molecular and Cellular Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Principal investigator, Director and Head of department (Molecular and cellular mechanisms of higher brain functions including learning and memory, pathogenesis of aging of the brain and neurogeneratative diseases such as Alzheimer's disease. Molecular mechanisms of functional brain development and neurodevelopmental disorders; learning disorders (LD), attention deficit hyperactivity disorders (ADHD), high functional autism, Aspergar syndrome). 1999- CREST "Endocrine disruptor" project, Principal Investigator

Thomas H. Hutchinson

Principal Scientist, Global Safety Assessment, AstraZeneca R&D, Sweden

Dr. Hutchinson is a biologist with nearly 20 years laboratory and field experience in the environmental risk assessment of pharmaceuticals and chemicals.. He has a BSc (Hons) in Environmental Sciences (King's College London) and PhD in Marine Biology (University of Plymouth). He has extensive practical experience in ecotoxicology, including endocrine disruption and wildlife immunology and has also conducted field work in Europe and Bermuda. He is an active member within several international groups, including the ECETOC Scientific Committee and OECD Validation Management Group for Ecotoxicology test guidelines. Dr. Hutchinson is currently working in molecular toxicology based at AstraZeneca's S:dert_lje, Sweden.

Reiko Kishi

Professor and Chair, Department of Public Health Sciences, Hokkaido University School of Medicine, Japan

<Educational Background> 1971 M.D., Hokkaido University, 1977 Ph.D., Hokkaido University. 1989 M.P.H, Harvard School of Public Health. <Professions> 1997-present Professor and Chair, Department of Public Health Sciences, Hokkaido Univ. School of Medicine. 1985 Associate Professor, Sapporo Medical Univ. School of Medicine. 1977 Instructor, Sapporo Medical Univ. School of Medicine. <Others> Member of Scientific Committee of Neurotoxicity and Psychophysiology, International Commission on Occupational Health (ICOH), Member, International Epidemiological Association (IEA), 2005 President of 64th Annual Meeting of Japanese Society of Public Health. Member of the board of directors, Japan Society for Occupational Health. Member of the board of directors, Japan Epidemiological Association Organizer. 2003 the Japanese Society of Cancer Epidemiology. <Award and Prizes> 2003 Outstanding Research Award, Japan Society for Occupational Health.

Junko Nakanishi

Director, Research Center for Chemical Risk Management, National Institute of Advanced Industrial Science and Technology (AIST), Japan

Prior to her professorship at AIST, she was a Professor at Yokohama National University and the University of Tokyo. She received her Doctor Degree in engineering from the University of Tokyo. Her research areas include environmental risk assessment and management and environmental policy. She was awarded Medal with Purple Ribbon by contribution in the field of environmental risk management study in 2003. Her representative publications include "Environmental Strategies for Water Systems" and "On Environmental Risk Study". She is a member of many distinguished governmental councils such as the Advisory Committee for Energy.

Iwao Uchiyama

Professor, Department of Urban and Environmental Engineering, Graduate School of Engineering, Kyoto University, Japan

Professor Uchiyama acquired the doctor of medical science after graduating from the University of Tokyo medical department in 1975. He was employed to the National Institute of Public Health in 1982, and was engaged in the research of health effects of air pollution or hazardous chemical substances. Then, he also studied the risk assessment of carcinogenic chemicals, and risk communication about health risk of chemicals. He has taken a present position from 2001. He was given the Japan Society for Atmospheric Environment Award in 2002, and the Japan Society of Risk Analysis Award in 2004.

Tomio Kinoshita

President, Koshien University, Japan

Professor Kinoshita graduated from Kyoto University in 1954 and received his Ph.D in social psychology in the Graduate School of Kyoto University. After graduation from Kyoto University he was appointed to his first post at Osaka Women's University after which he returned to Kyoto University as a full professor. There he performed his duties as Dean of the College of Liberal Arts and Sciences and Dean of the College of Integrated Human Sciences. After retiring from Kyoto University he was appointed President of Koshien University, Hyogo Prefecture. His major fields are social psychology and risk psychology, especially group processes, social communication, social rules, crowd behavior, political behavior, risk communication, risk perception, and risk management. He has received several awards from the Society for Risk Analysis, Japan Section, and from the Behaviormetric Society of Japan, as well as other honors.

Toshiko Kikkawa

Associate Professor, Faculty of Business and Commerce Keio University, Japan

1988: Graduated from Kyoto University, Faculty of Letters. 1989: Assistant Professor at Kyoto Gakuen University, Kyoto, Japan. 1995: Assistant Professor at University of Tsukuba, Tsukuba, Japan. 1998: Associate Professor at Keio University, Tokyo, Japan. 1999: Received Ph.D. from Kyoto University in Psychology. <Specialized Fields> Risk communication, Simulation games <Major publications> Risk communication. Fukumura Shuppan (in Japanese) (1999). Dealing with risks. Yuhikaku (in Japanese) (2000). Risk communication between mineral property developers and local communities. (co-authored) Mining Journal Books, Ltd.: London (2003).

Hiroo Yamagata

Reviewer, Translator, Japan

Yamagata Hiroo received his masters degrees from University of Tokyo (urban engineering) and Massachusetts Institute of Technology (real estate development). Currently works as a foreign aid consultant mainly in the power and road sector, although better known as one of the best English-Japanese translators in Japan, and an overly straightforward critic, covering an extremely wide range of disciplines including literature, computers, economics and finance, environment and youth culture. His strength is in interdisciplinary issues, with his clear writing style is often both praised and criticized for making issues "too clear and understandable." His translations include Paul Krugman "The Age of Diminished Expectations", and Bjorn Lomborg "The Skeptical Environmentalist". Author of "Slashing Ideas," and "Just a Book on William Burroughs," among others.

Saburo Matsui

Professor, Graduate School of Global Environmental Studies, Kyoto University Councilor of Kyoto University, Japan

Professor Matsui has been conducting various researches on micro-pollutants in water more than 30 years. He has achieved important works in the field of biological wastewater treatment for decomposing hazardous chemicals including petrochemical and chemical industries. He contributed the knowledge of the activated sludge degradability method in the Japanese policy of Chemical Toxicity Assessment. Persistent organic pollutants are generated in chemical industries and discharged in wastewaters. Management of industrial wastewaters is still a remaining issue in terms of POPs control in the global perspective. He also developed a bacterial DNA toxicity method for the evaluation of river, lake and wastewaters as well as drinking water in terms of mutagen and DNA toxic chemicals, which is called the Bacillus subtils Rec-assay. The Rec-assay is a useful method for detection of micro-pollutants in any water samples. Among micro-pollutants in water, hydrophobic ones are important potential group of DNA toxicity. He was awarded for the Vollenweider Lectureship in Aquatic Sciences, by the contribution of the Rec-assay from Canadian National Water Research Institute, Environment Canada, 1995. He started research on endocrine disrupting chemicals in the environment since 1996. He has contributed mainly in the two areas: Identification and evaluation of human estrogen contamination in water: Evaluation of endocrine disrupting chemicals in water in terms of the AhR activation. The finding of indirubin and indigo in human urine has contributed in the development of a new horizon of investigation of toxic mechanism of POPs, specially PAHs including TCDD, PCBs, Benzo(a)pyrene, etc. The reporter gene assay of AhR is a useful technique to detect and evaluate POPs in the environment. He is the leader of the National Research Group on Risk Assessment of Endocrine Disruptors in the Environment, Granted by Ministry of Science & Education, Japan, 2000-2004. This group consists of 90 teams of 150 scientists of universities and national research institutes. The budget size of the grant is about US $ 6 million in total. The group consists of six subgroups including Human Exposure and Risk, Wild Animal Exposures and Risk, Toxicology, Metabolism of Endocrine Disrupting Chemicals, Bioassay and Biomarker, and Risk Evaluation and Management. The group is generating many useful findings and techniques in the research fields of endocrine disrupting chemicals in the environment.

Takashi Higaki

Journalist, Writer, Japan

中西　準子

独立行政法人 産業技術総合研究所
化学物質リスク管理研究センター長 工学博士

専門は、専門環境工学、環境リスク管理学。横浜国立大学工学部卒。東京大学工学系大学院博士課程修了。東京大学助手、同教授、横浜国立大学教授を経て、現職。著書に、『環境リスク学』（日本評論社）など。

内山　巌雄

京都大学大学院工学研究科 都市環境工学専攻 教授

1975年（昭和50年）東京大学医学部を卒業後、医学博士を取得。内科医を経た後1982年（昭和57年）より国立公衆衛生院研究員，同労働衛生学部長を経て、2001年（平成13年）から現職。主に大気汚染物質の生体影響に関する研究に従事し、最近は発がん性化学物質のリスクアセスメント，化学物質に関するリスクコミュニケーションの研究を行っている。大気環境学会学術賞（2002年（平成14年））、日本リスク研究学会賞（2004年（平成16年））を受賞。

木下　冨雄

甲子園大学 学長

1954年 京都大学文学部（心理学専攻）卒業。1956年に京都大学大学院文学研究科修士課程修了後、京都大学助手、大阪女子大学助教授，京都大学助教授を経て同教授，京都大学教養部長、京都大学総合人間学部長を歴任。1993年 京都大学名誉教授。その後、関西大学経営情報学部教授を経て、1997年に甲子園大学学長、現在に至る。日本社会心理学会元理事長、日本リスク研究学会元会長。文学博士。専門は社会心理学とリスク分析。

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1982年（昭和57年）京都大学文学部卒業、1988年（昭和63年）京都大学文学研究科博士課程後期単位取得退学。現職：商学部助教授。主要研究テーマ：リスク・コミュニケーション。主要論文等：『リスク・コミュニケーション　相互理解とよりよい意思決定をめざして』1999福村出版、『リスクとつきあう－危険な時代のコミュニケーション』2000

山形　浩生

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東京大学都市工学修士、およびマサチューセッツ工科大学不動産開発修士。海外援助のコンサルタントとして主に電力・道路部門で活動しているが、文学、コンピュータ、経済やファイナンス、環境、文化など恐ろしく多様な分野での翻訳家および著述家としても有名。特に境界領域的な分野で強みを発揮し、その明快な書きぶりはしばしば「わかりやすすぎる」と批判されるほど。主な翻訳にクルーグマン『クルーグマン教授の経済入門』（日経文庫）、ロンボルグ『環境危機をあおってはいけない』（文藝春秋）など。著書に『新教養主義宣言』（晶文社），『たかがバロウズ本。』（大村書店）など。

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1966年（昭和41年） 京都大学衛生工学科卒、1968年（昭和43年） 同大学院修士課程修了。1972年（昭和47年） アメリカ合衆国テキサス大学オースチン校博士課程修了Ph.D.（土木工学）。1972年（昭和47年） 茨城県鹿島下水道事務所技師（主幹）、1975年（昭和50年） 金沢大学土木工学科助教授。1986年（昭和61年） 京都大学衛生工学科助教授、1987年（昭和62年） 京都大学工学部附属環境微量汚染制御実験施設教授。1995年（平成7年） 京都大学大学院工学研究科附属環境質制御研究センター教授。2001年（平成13年） 京都大学大学院工学研究科環境工学専攻環境デザイン工学講座教授、2002年（平成14年） 京都大学大学院地球環境学堂環境調和型産業論教授、現在に至る。2002年（平成14年） 日本水環境学会「学術賞」、2004年（平成16年） 環境システム計測制御学会「奨励論文賞」受賞。

日垣　隆

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1958年生まれ。東北大学法学部卒業。日本のマスメディアで初めてダイオキシン騒動の行き過ぎを指摘（『文藝春秋』1998年10月号）。広告料の多さを基準に有名商品を全否定したベストセラー『買ってはいけない』に対して初めて科学的データに基づき批判（同誌1999年９－10月号）。環境ホルモンによる精子激減説にも検証を加え異論を唱えた（『それは違う！』第6回文藝春秋読者賞）。他の著書に、『情報の技術』（朝日新聞社）、『偽善系Ⅰ・Ⅱ』（第7回編集者が選ぶジャーナリズム賞）、『そして殺人者は野に放たれる』（第3回新潮ドキュメント賞受賞）など多数。現在「週刊エコノミスト」「中日新聞」など14紙誌で連載中。科学者との対談番組（TBSラジオ）のMCも７年目。中西準子氏らとの共著『いのちを守る安全学』（新潮文庫）も。

第7回 内分泌攪乱化学物質問題に関する国際シンポジウム

International Symposium on Environmental Endocrine Disrupters 2004

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Session 1 Basic Science

Effects of Suspected Endocrine Disruptors on Nuclear Receptor Family -*Involvement of RXR in Gastropod Imposex Caused by Organotins*-

Jun-ichi Nishikawa
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Nuclear receptors play important roles in the maintenance of the endocrine system, regulation of organ differentiation and fetal development. Endocrine disruptors exert their adverse effects by disrupting the endocrine system via various mechanisms. To assess the effects of endocrine disruptors on nuclear receptors, we developed a high-throughput method for identifying activators of nuclear receptors. Using this system, we found that several compounds possess agonistic activities for multiple receptors simultaneously. Butyl benzyl phthalate, hexachlorocyclohexane, maneb, mancozeb, and alkylphenols were weakly agonistic for multiple receptors including estrogen receptor. One intriguing finding was that the effect of organotins on retinoid X receptor (RXR) was as strong as that of its endogenous ligand, 9-cis retinoic acid (9-cis RA). Organotins are potent inducers of imposex in marine gastropods. Cloning of the RXR homolog from wild rock shell (Thais clavigera) revealed that the ligand-binding domain of rock shell RXR was very similar to vertebrate RXR and bound to both 9-cis RA and to organotins. Further, injection of 9-cis RA into females of Thais clavigera induced the development of imposex. These data provide strong evidence that RXR plays an important role in inducing the development of imposex, namely the differentiation and growth of male genital tracts in female gastropods.

Roles of AhR in Endocrine Disruptive Effects by Polycyclic Aromatic Hydrocarbons

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AhR is originally identified as a transcription factor which regulates the expression of xenobiotic-metabolizing enzymes in response to polycyclic aromatic hydrocarbons (PAH).

Gene disruption experiments of AhR revealed that AhR is also involved in teratogenesis of cleft palate and hydronephrosis caused by TCDD, carcinogenesis of skin by benzo(a) pyrene and others.

In DNA transfection assay using an HRE-driven reporter gene of luciferase, 3-methylcholanthrene (3MC) activated the expression of the reporter gene in the presence of AhR, Arnt and ER without estradiol (E_2) in COS7 cells and MCF7. This enhancement of the reporter gene expression was dependent on AhR/Arnt, ER and ERE in the promoter region. On the other hand, addition of E_2 activated even higher expression of the reporter gene, while the presence of 3MC lowered the elevated expression of the reporter by E_2. The same expression profile was also observed *in vivo* with the ER-target genes such as c-fos and VEGF in the ovariectomized (OVX) female mice. 3MC enhanced the expression of these target genes in the liver of OVX mice and this enhancement was dependent on the presence AhR/Arnt and ER, because this enhancement was lost in AhR- and ER-KO mice. Uterus weight was increased significantly by treatment with 3MC and this weight gain was also dependent on AhR/Arnt and ER. GST-pulldown assay indicated that in this estrogenic effects by 3MC, 3MC-activated AhR works as a coactivator of unliganded ER on the promoter of the ER-target genes to activate their expression.

It has been known that AhR-KO female mice are defective in reproduction. We investigated this defective reproduction of AhR-KO female mice and found that this defect was due to aberrant estrus cycle which was caused by defective synthesis of E_2 in ovaries of AhR-KO mice. RT-PCR analysis of the mRNA for steroidogenic enzymes in the ovary revealed that only P450 aromatase *(CYP19)* gene was downregulated in the AhR-KO mice.

Survey of the sequence localized the XRE sequence in the promoter region of mouse and human *CYP19* genes. DNA transfection assay using the reporter gene consisting of the luciferase and the promoter sequence of the *CYP19* gene clearly demonstrated that the reporter gene expression was enhanced by DMBA (dimethyl benzoanthracene) in the presence of AhR/Arnt and Ad4BP/SF-1. The Chip (chromatin immuno-precipitation) assay confirmed that the XRE and Ad4 sequences recruited their respective transcription factors, AhR/Arnt and Ad4BP/SF-1, which interacted with each other on the chromatin.

Taken together, these results indicate that ligands to AhR exhibit their estrogenic effects by two ways: one is that AhR which is activated by binding with the ligand directly enhances the expression of CYP19 together with Ad4BP, resulting in increased synthesis of E_2 from testosterone and the other is that the ligand-activated AhR serves as a coactivator of ER α and β to enhance the expression of the ER-target genes.

Thyroid Hormone, Brain Development, and the Environment

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Thyroid hormone is essential for proper brain development in humans and in animals. Therefore, any environmental chemical that interferes with thyroid hormone action in the developing brain may produce adverse consequences. However, our ability to identify developmental neurotoxins that act by interfering with thyroid hormone signaling is compromised because the role of thyroid hormone in brain development is not well understood, and because the mechanisms by which toxicants can interfere with thyroid hormone signaling may not produce effects that are clearly attributable to thyroid disruption. We have focused our work on understanding the role(s) of thyroid hormone in brain development, and on investigating the relationship between the ability of thyroid toxicants to reduce circulating levels of thyroid hormone and to interfere with thyroid hormone signaling in the developing brain. This work has revealed some interesting paradoxes that will inform epidemiological studies and risk analysis strategies. For example, polychlorinated biphenyls (PCBs) can augment thyroid hormone action both in vivo and in vitro, but they do not bind to the thyroid hormone receptor in the T3 binding domain. We are employing ChiP assays to test the ability of PCBs to selectively augment T3 action on gene expression in vivo. Bisphenol A, in contrast, binds to the thyroid hormone receptor, but appears to selectively antagonize the beta TR. There are very important implications of these findings.

Estrogenic Disruption of the Male Urogenital System

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The process of organ differentiation represents a critical period in reproductive system development. During this time tissues are particularly susceptible to the disruptive effects of estrogenic chemicals that have the capacity to bind to intracellular steroid receptors and alter the effects of endogenous steroid hormones. While exposure to estrogenic chemicals may occur during critical stages of fetal life, the consequences of such exposure are typically not recognized until well into adulthood when problems relating to functioning of the reproductive system become apparent.

Previous studies indicate that estrogen may play a role in modulating the effects of androgen on the differentiation and growth of the accessory sex glands in males. For example, alterations in the circulating levels of estrogen during fetal development can produce permanent changes in the response to androgen. Our long-term goal is to determine the consequences of low dose exposure to endocrine disrupters, particularly environmental estrogens, during fetal prostate development.

We examined regional growth effects in the urogenital sinus (UGS) following exposure of male mouse fetuses to a low, physiologically relevant dose of several estrogenic compounds, including a component of polycarbonate plastics, bisphenol A (BPA); a pesticide, methoxychlor (MXC); and an oral contraceptive component, ethinylestradiol (EE). We fed pregnant mice these estrogens from gestation day 14-18 at doses (bisphenol A = 10 μ g/kg/day; EE = 0.1 μ g/kg/day) below the average level of human fetal exposure, and as a positive control we also administered a low dose of diethylstilbestrol (DES) at 0.1 μ g/kg/day. In addition, we administered DES at a very high dose of 200 μ g/kg/day. We examined the prostate and urethra in the cranial region of the urogenital sinus (UGS) in gestation day 19 mouse fetuses.

In male fetuses the low doses of all three estrogenic chemicals produced virtually identical increased proliferation of the UGS epithelium associated with an increase in the number and size of the developing prostate ducts, malformation of the colliculus region of the prostate, and constriction of the urethra as it enters the bladder neck. These estrogens stimulated additional gland formation and epithelial hyperplasia in the dorsolateral but not the ventral prostate. High doses of DES inhibited dorsolateral prostate formation. Proliferating cells were mainly associated with the proximal region of the ducts and also expressed markers of the basal cell phenotype. This is consistent with the hypothesis that basal cells (or a subset of these cells) provide the proliferative pool for the developing prostate ducts and may represent a population of cells in the prostate epithelium that is particularly sensitive to estrogen stimulated cell growth. The long-term effects of fetal exposure to estrogen mimics on adult reproductive organ development in an animal model would indicate concern for the consequences of similar human low dose exposure to the same estrogenic chemicals.

Expression Profiling EDC Actions in the Brains of Aquatic Vertebrates: Approaches and Challenges

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Considerable experimental evidence indicates that most organs and tissues will respond to xenohormones and environmental contaminants. However, there are far fewer environmental and toxicological studies on the neuroendocrine brain than other tissues, especially in non-model, non-mammalian species. We have used differential display to obtain candidate targets for estrogenic EDCs in snapping turtle and leopard frog tadpole brain. While this approach can be useful, especially for animals whose genome has not been sequenced, data must be carefully and cautiously interpreted and confirmed with other methods. To understand the range of impacts steroid hormones may have on brain function, we are developing AURATUS, a multifaceted resource for cDNA microarray analysis of gene expression in the goldfish. To date approximately 500 verified cDNAs have been sequenced. Treatment with testosterone upregulated several transcripts, in particular isotocin and an uncharacterized EST. We have also used reporter gene assays. In vivo somatic gene transfer of an ERE-luciferase construct to Xenopus laevis tadpole and adult goldfish brain was used to determine if low levels of ethinyl estradiol affects gene expression in situ in the brain. In both species EE2 increase luciferase activity 2-fold. Fibrate drugs act on nuclear peroxisome proliferator activated receptors (PPARs) and all 3 subtypes (alpha, beta and gamma) are expressed in fish brain. We have not yet determined if fibrate drugs affect gene expression in the fish brain but we have established that a mammalian PPRE-luciferase construct transfected into fish cells is activated by bezafibrate, indicating that fish PPARs respond to these drugs. Bezafibrate also suppresses testosterone levels in male goldfish. The presence of fibrates in sewage effluents and in waterways raises the possibility that they may affect neuroendocrine processes in aquatic vertebrates. Some of these approaches will be reviewed with the intention of highlighting both their advantages and disadvantages for the assessment of potential EDC actions in the brain. Supported by NSERC, CNTC, MNHN-Paris.

Session 2 Wildlife

Endocrine Disruption in a Small Cladoceran Crustacean

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The endocrine systems of invertebrates differ from those of vertebrate organisms both in the type of endocrine glands present and in the chemical structure of specific hormones that are produced. Because invertebrates constitute the vast majority of animal species on earth, it is urgently necessary to develop a screening program that assays endocrine disrupting chemicals for invertebrates and to study the mechanisms associated with endocrine disruption in invertebrates.

Freshwater cladoceran crustaceans usually inhabit lakes and ponds as zooplankton. They reproduce only through females (parthenogenesis) as long as environmental conditions are favorable. Males appear in adverse conditions such as food shortage, high population density, or short photoperiod and mate with females that have sexual eggs. The fertilized sexual eggs develop into resting eggs, which are resistant to desiccation and freezing.

Daphnia magna is one of the most popular cladoceran animals used in toxicity tests because it is easily handled owing to its relatively large body size and short generation time.

Twenty-one-day reproduction experiments revealed that exposure to 10 chemical substances, all of which were juvenile hormones, or their analogs, in insects or crustaceans, induced the production of male neonates in *D. magna* in a concentration dependent manner. Induction of male sex in neonates by exposure to juvenile hormones and their analogs was observed not only in *D. magna*, but also in other species in different taxonomical groups - genera *Moina* and *Ceriodaphnia*. This suggests that juvenile hormone is involved in initiating male production, followed by sexual reproduction, in most cladocerans that exhibit cyclic parthenogenesis.

From the results of short exposure experiments, the stage when eggs are in the ovary prior to their release into the brood chamber was estimated to be the period susceptible to the juvenile hormones and their analogs.

Development into males was not induced by exposure to bisphenol A, nonylphenol, or octylphenol, known disruptors of vertebrate endocrine systems, at concentrations that caused reduction in the reproduction rate. 20-Hydroxyecdysone, a molting hormone in invertebrates, induced a high mortality rate in test animals at high concentrations but neither reduced the reproduction rate nor increased the rate of development into males. These results indicate that the development of D. magna into males is not caused by chemical stress but by endocrine disruption.

Little is known about the mechanisms associated with production of male neonates induced by juvenile hormones and their analogs. Our findings will be the first step toward elucidating the mechanism of environmental determination of sex in cladocerans, as well as providing the basis of a new screening method for potential juvenile hormone disrupting effects and for evaluating endocrine disrupting phenomena in crustaceans.

Effects of Low Bisphenol A Concentrations in Prosobranch Mollusks

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Prosobranch snails like the freshwater ramshorn snail *Marisa cornuarietis* develop a complex syndrome of morphological and physiological alterations when exposed to xeno-estrogenic compounds such as bisphenol A (BPA), termed as the induction of "superfemales". Affected specimens are characterized by the formation of additional female organs, an enlargement of the accessory pallial sex glands, gross malformations of the pallial oviduct section resulting in an increased female mortality, and a massive stimulation of egg and clutch production

During a first series of laboratory experiments it has been shown that BPA concentrations in a nominal concentration range from 1 - 100 µg BPA/L induced superfemales in *Marisa* in a 5 month experiment with adult snails and a complete life cycle test for 12 months. Although the study indicated effects already at the lowest test concentration, the results were not used for the current BPA risk assessment process in the European Union due to shortcomings in the experimental design.s

It was therefore our objective to derive a valid NOEC or EC_{10} value in additional experiments and to analyze the appropriateness of experimental conditions in a planned industry repeat study. In a first series of exposure experiments a nominal concentration range from 0.05 - 1 µg BPA/L (with analytical control) was applied and the influence of the reproductive phase of the snails on the study outcome analyzed. A second series of experiments was performed in a nominal concentration range from 0.25 - 5 µg BPA/L (with analytical control) at two temperatures (20℃ and 27℃) in parallel. This series focused on the temperature dependence of BPA effects and whether the BPA-induced superfemale syndrome is estrogen receptor mediated. Ethinylestradiol (EE_2) was used as a positive control. Based on measured concentrations, a LOEC of 48.3 ng/L, a NOEC of 7.9 ng/L and an EC_{10} value of 13.9 ng/L were calculated. The results regarding dependence of BPA effects from reproductive status of the snails and the applied temperature will be presented as well as the specificity of the superfemale syndrome for an estrogenic action.

The study shows that prosobranch snails are affected by BPA at lower concentrations compared to other systematic taxa in the animal kingdom. For the achievement of a sufficient protection of wildlife in aquatic ecosystems effect data from these experiment have to be considered for the BPA risk assessment process in the European Union.

Investigations for this study were funded by the German Federal Environment Agency (project code 29765001/04) and the European Union within the COMPRENDO project (contract no. EVK1-CT-2002-00129).

Oestrogen and Androgen Receptor Agonists: Identification and Measurement of *in vitro* Activity in the Aquatic Environment

Kevin V. Thomas, M.R. Hurst, J. Balaam and J.E. Thain

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Effects consistent with exposure to oestrogenic and androgenic substances have been observed in wild fish populations. This has been predominantly observed as the occurrence of elevated plasma vitellogenin (VTG) concentrations in certain freshwater and estuarine species (e.g. flounder). In order to assess the risk that oestrogenic and androgenic substances pose to the aquatic environment, and to regulate activities that may be releasing such compounds, there is a need to identify which compounds are responsible for these effects. It is possible to identify the compounds responsible for *in vitro* effects by using a combination of *in vitro* receptor based assays and chemical analysis. For example, steroid oestrogens have been identified as responsible for the majority of the activity seen in marine sewage treatment works (STW) effluents. Targeted chemical analysis and bioanalytical monitoring can then be applied to assess the effectiveness of additional treatment processes in reducing the oestrogenic activity of STW effluents. This and other applied examples are used to show how oestrogenic and androgenic substances can be identified in the environment, how bio- and chemical analysis can be used to assess their effects in the environment and how the information obtained can be used in both regulatory and policy frameworks.

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Evidence Derived from Field Surveys that Indicates Estrogenic Endocrine Disruption is Widespread in the Marine Environment

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The CEFAS laboratory in Lowestoft carried out the pioneering field surveys of rainbow trout in the late 1980s that provided the first proof that the freshwater environment was contaminated with estrogenic compounds. This proof came in the demonstration of elevated vitellogenin (VTG) levels in the blood plasma of caged trout that were placed in certain UK rivers (Purdom et al., 1994; Chemistry & Ecology 8, 275-285) - especially in the vicinity of sewage treatment works. In 1996, CEFAS, funded by DEFRA, turned their attention to estuaries - carrying out extensive collection and assay of VTG in blood plasma of a migratory flounder *(Platichthys flesus)*. It was immediately discovered that several estuaries in the UK were heavily contaminated with estrogens. It took several more years to show that levels of contamination were declining in at least two of the estuaries and also to unexpectedly reveal that the impact of the contamination was highly seasonal - affecting the males more severely in the winter than in the summer. In 2002, CEFAS started to look for evidence of estrogenic endocrine disruption in the Atlantic cod *(Gadus morhua)*, a species that lives its entire life cycle in the open sea. Collections of cod have now been made from several areas on the continental shelf. In at least three of these areas (off Iceland, the Shetland Box and the southern North Sea) male cod have been found with elevated levels of VTG. Furthermore, elevated VTG levels in males show a strong positive correlation with the size of the fish. These findings raise several questions, the main ones being: are elevated VTG levels a sign of endocrine disruption or of a natural aging process in males? is endocrine disruption linked to the sharp decline of this species in the North Sea? The second question cannot be answered until we know the answers to the first. The synthesis of VTG by the liver requires estrogen stimulation. Thus, if VTG in males were a natural process, we would expect to find 17β-estradiol in the plasma of those males that also have elevated VTG. This we have not found (and nor have we found any of these males to be intersex). It thus seems probable that the causative agent is of external origin. Furthermore, the positive relationship to the size of the fish provides a strong clue that the endocrine disrupters are entering the fish via the food chain rather than by direct absorption from the water. It is well known that cod alter their diet as they grow (to eventually become 'top predators'). We will draw on work in Japan and Europe to argue not only that estrogenic endocrine disruption is common in the marine environment but also that diet is far more important as a source of endocrine disrupters than previously suspected - calling into question the numerous risk assessments that are based on exposure of fish to compounds that are delivered via the water only.

Organotin Compounds are Potent Inducers of Adipogenesis in Vertebrates

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Organotin compounds have been widely used as antifouling agents for ships, as stabilizers in plastics manufacturing and as fungicides on food crops. Aquatic invertebrates, particularly marine mollusks, are extremely sensitive to trialkyltin compounds such as tributyltin (TBT) chloride and undergo changes in sexual identity in response to exposure. This has led to the ban of such compounds in antifouling paints in a number of countries, although organotin compounds continue to be widely used for other purposes. Organotin compounds are known to have neuro and immunotoxic effects in vertebrates although the complete spectrum of activity has not been characterized. We have recently found that certain organotin compounds such as TBT are potent and efficacious activators of the vertebrate retinoid 'X' receptor (RXR), a nuclear hormone receptor that acts both as a ligand modulate transcription factor and also as a common partner for many other nuclear hormone receptors. TBT binds to and activates RXR with nanomolar affinity establishing TBT and its congeners as bona fide RXR ligands. Surprisingly, the major phenotype observed when frog or mouse embryos were treated with TBT did not involve sexual differentiation as in mollusks. Rather, treatment of frog or mouse embryos with TBT or synthetic RXR activators elicited a dramatic increase in the number of adipocytes and led to the apparent conversion of hepatic and gonadal tissue into adipocytes. Microarray analysis of mice treated embryonically with TBT revealed a striking increase in the expression of markers of adipocyte differentiation. Many of the same genes were also upregulated in frog embryos treated with TBT. The same genes were also upregulated in adult male mice treated with TBT, suggesting that both embryos and adults are sensitive to the adipogenic effects of TBT. Our results establish a novel and unexpected role for TBT and RXR activators in adipocyte differentiation and suggest that organotins exert potent and undesirable effects on vertebrate physiology, in addition to their known detrimental effects on invertebrates.

Noises of Genetic Variation in Estimating Effects of Environmental Factors in Animals: A Review

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An individual phenotype or its respective characters are a result of genetic and environmental factors through development to death of animals. Here, environmental factors involve not only commonplace environments but also very specific experimental conditions or an artificially disrupted environmental condition. While expression of some characters is determined mainly by a genetic factor, that of another characters is largely affected by a specific environmental condition. Therefore, genetic variations at various levels of animal groups, as from individuals to species, have to be considered in an evaluation of environmental effects on animals, and the estimated result may carefully be extrapolated to a case of human as one of the animal species.

1) **Phenocopy;** When a phenotypic variant, that is phenotypically same as a certain genetic mutant, can be induced from the genetically normal individuals by an experimental treatment or under a specific environmental condition, the phenotypic variant is called as a phenocopy of the genetic mutant. (Goldschmmidt, 1924-1926 at Univ. of Tokyo)
2) **An idea in Experimental Teratology;** "It is considered possible that every phenotype of genetic mutants can be induced by a specific experimental condition (or by disruption of normal genes expression under a specific environmental condition) (Kondo, 1965)."
3) **Geneticist's viewpoint;** An individual phenotype is determined by genetic factors and/or environmental factors.
4) **Examples for relationships between environmental/experimental conditions and animal genetic variations;**
   a. Different incubation period after BSE-inoculation by strains of mouse (Bruce *et al.*, 1994).
   b. Different teratogenicity by species, mice and house musk shrews (Inoue *et al.*, 1985).
   c. Different teratogenicity both by experimental condition and species, mice and house musk shrews (Inoue *et al.*, 1985).
   d. Different induciability of rumplessness phenocopy by breeds of chicken (Landaur, 1945, 1948).
   e. Diffrent induciability of rumplessness phenocopy by maternal genetic effect (Landaur, 1948).
   f. Spontaneous genetic mutation and genetic load of individuals in a population (Li, 1955).
5) **Importance of further field-studies, and a possible example;** Previous big fact-findings obviously show the significance of field studies of environments even under unknown complex conditions. Feral pigeons *Columba livia* inhabit through the world, even heavily disrupted environments. The population structure and density, life style, oviparity, *etc.* may be favored as an indicator of environmental conditions.

Session 3 Exposure

Phenolic Endocrine Disrupting Chemicals (Alkylphenols and Bisphenol A) in Asian Waters

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Phenolic endocrine disrupting chemicals (EDCs) are widely used in industrialized societies. Intensive surveys of the EDCs in industrialized countries during last several years demonstrated that phenolic EDCs are widely distributed in aquatic environments due to their widespread usage. However, very little information on the distribution and behavior of phenolic EDCs is available in South and South East Asia. Thus, we conducted monitoring of phenolic EDCs in the Asian waters. In the presentation, two aspects of the phenolic EDCs contamination in South East Asian waters will be introduced.

Phenolic EDCs in leachate from garbage dumping sites in South East Asia

Phenolic EDCs (NP, OP, BPA) were measured in leachates from 11 landfill sites in five Southeast Asia countries including Malaysia, Philippines, Thailand, Vietnam, and Cambodia. Extremely high concentrations of BPA ranging from 2.3 μg/L to 4300 μ g/L were detected in the leachates. Combined with our measurement of natural estrogens (E1, E2, E3) in the leachates, estradiol-equivalent concentrations (EEQ) were calculated for all the target compounds and compared each other. In most leachates, contribution of BPA to total estrogenic activities was predominant over the other compounds including natural estrogens. Our monitoring demonstrated that leachates form garbage dumping sites could be major contributors of EDCs to aquatic environments in South East Asia. More extensive monitoring focusing on the dumping sites and surrounding environments are urgently necessary as well as installing sustainable leachate treatment systems to the dumping sites.

Accumulation of phenolic EDCs in mussels

Using mussels and seawater collected from Tokyo Bay, bioconcentration factors (BCFs) was determined for the phenolic EDCs. In mussel samples, NP was most abundant with the concentration range from 47 to 1347 ng/g-dry tissue. NP concentrations were several times higher than PCBs. OP and BPA concentrations were one to two orders of magnitude lower than NP. Based on the EDC concentrations in the seawater and the mussel tissue, BCFs were calculated. Lipid-base BCF of NP, OP, and BPA was ~ 10^5, ~10^4, and ~10^3, respectively. These values were similar to octanol-water partition coefficients (Kow) for individual compounds, indicating that the EDCs are bioconcentrated through their partitioning between the biological lipid and the surrounding water.

Green mussel samples collected from India, Indonesia, Malaysia, Singapore, Thailand, Vietnam, Cambodia, and the Philippines were analyzed for the phenolic EDCs. At several locations in S&SE Asia, elevated concentrations of EDCs were observed. The high NP concentrations up to 600 ng/g-dry tissue found in Malaysia, Singapore, the Philippines, and Indonesia were comparable to those in Tokyo Bay. BPA concentrations found in one location in India exceeded the highest concentration in Tokyo Bay. No elevated EDCs concentrations were observed in Vietnam and Cambodia, probably due to the lower levels of industrialization in those countries.

Human and Wildlife Exposures to Persistent Brominated Flame Retardants

Åake Bergman

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Brominated flame retardants (BFRs) have become increasingly important in the technosphere during the last two decades. Still the BFRs are only making up less than twenty per cent of all flame retardants being used. The production volumes are still high, exceeding 200.000 tons annually on a global scale. Among approximately twenty BFRs in production three basic structures form the basis for the major BFRs. The far most used BFR is tetrabromobisphenol A (TBBPA) and its three neutral derivatives, diallyl, dibromopropyl and diglycidyl ether, respectively. The second most used BFR is DecaBDE, almost entirely consisting of perbromodiphenyl ether (BDE-209), and third hexabromododecane (HBCDD). Other BFRs of interest are the OctaBDE and PentaBDE, both consisting of PBDE mixtures with different content of bromine. The use of these two PBDE products has been regulated within EU during 2004. Still all PBDEs are present in a huge number of commercial products that are slowly moving towards their end of life. The BFRs are distributed to the environment and humans are exposed to BFRs both directly via inhalation at home and at work and indirectly via their food. The major BFRs present in wildlife, domestic animals and in humans are PBDEs including all PBDEs up to the decaBDE and HBCDD, while TBBPA is less abundant in humans and in wildlife.

The human exposure to PBDEs, as measured in blood serum or plasma, and in milk, is different in different parts of the world. Humans living in Japan and Europe have in general low concentrations unless the persons are subjected to occupational exposures. The general populations have in general below 10 ppb lipid base concentrations while the situation is much different in North America with a large number of subjects with levels above 100 ppb, even up above 1000 ppb has been reported. The PBDEs have been found to increase in mothers' milk from different countries. Recently there are strong indications of a trend shift in the PBDE pattern showing a hexaBDE, BDE-153, to be the major PBDE congener in humans, instead of BDE-47 - a tetrabrominated diphenyl ether. DecaBDE is bioavailable and the Swedish concentrations are nowadays similar to BDE-47. BDE-209 is indicated to degrade to lower brominated congeners in humans and it has a half-life of approximately 14 days in man. BDE-209 has become more commonly reported in mammals, fish and birds as more laboratories have started to look for it. Since present in fish, chicken and dairy products BDE-209 is also ingested by humans via the food. Human levels of BDE-209 above 100 ppb has been reported both for occupationally and randomly exposed humans. Increasing time trends have been shown for HBCDD in guillemot eggs from the Baltic Sea. No temporal trends are reported for HBCDD in humans even though reported in people from Sweden, The Netherlands and Mexico. Several of the BFRs have been associated with endocrine related effects.

PCB Metabolites in Humans with Focus on OH-PCBs and $MeSO_2$-PCBs

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Stockholm University, Sweden

Shortly after PCBs first were identified as ubiquitous environmental contaminants they were also found to undergo metabolism and forming hydroxylated PCBs, more correctly referred to as polychlorobiphenylols (OH-PCBs). However, these metabolites were initially regarded as excretion products and consequently of less importance. It was not until the 1980s' when OH-PCBs were found to be retained in the body they become more interesting. OH-PCBs are excreted and may be present in the intraluminal uterine fluid but most important is their retention in the blood. OH-PCBs are retained in fish, bird, and mammalian blood at high concentrations. Hitherto approximately fifty OH-PCBs have been identified in human blood with some five congeners being the most prevalent metabolites in the blood. These are 4-OH-CB107, 3-OH-CB138, 4-OH-CB146, 3-OH-CB153 and 4-OH-CB187, metabolites that are present in concentrations of up to hundreds of ppb, e.g. the last congener is present at median levels of 100-150 ng/g l.w. in human serum from subjects sampled in Slovakia and in the Faroe Islands. Individual OH-PCB concentrations in humans and in wildlife are often higher than the concentrations of individual PCB congeners, of course excluding the most prevalent PCB congeners. 4-OH-CB107 and 4-OH-CB187 have blood half-lives in rats of 4 and 15 days, respectively, that indicate that we can expect the latter to have between 2 and 3 months in humans. These two OH-PCBs have been more thoroughly investigated in relation to its endocrine related effects and found to influence the thyroid hormone homeostasis and oestrous cyclicity.

PCBs do undergo Cytocrome P450 mediated oxidations leading to the formation of reactive arene oxide intermediates. These arene oxides may be rather stable as in the case of 2,2',5,5'-tetraCB 3,4-oxide while much more reactive in others. The arene oxides of PCBs may react with biomacromolecules or undergo further oxidations to quinones, metabolites that similarly to the arene oxides are very electrophilic species. The arene oxides are precursors of PCB dihydrodiols, OH-PCBs, formed with or without a 1,2-shift, and PCB methyl sulfones ($MeSO_2$-PCBs) after reaction with glutathione, mercapturic acid pathway transformation, C-S-lyase cleavage of the sulphur-cysteine carbon bond, methylation and oxidation.

$MeSO_2$-PCBs are formed from the most reactive PCBs, compounds with at least one meta-para-position free for oxidation. Hence the metabolites have a higher persistency than the maternal PCB compound. Still, both wildlife and human concentrations of $MeSO_2$-PCBs are lower than for the most abundant OH-PCBs. $MeSO_2$-PCBs are present at low ppb or less on a lipid weight basis in humans even when exposed to PCBs. This makes the occurrence of these metabolites in humans of less importance than the OH-PCB metabolites. Still, it is interesting to note that several $MeSO_2$-PCBs are optically active with a total dominance of one atropisomer over the other, as observed in e.g. grey seals. The PCB methyl sulfones have some very different enzyme induction properties; they accumulate specifically in human and wildlife lungs and in particular in the liver.

Rating Risks of Chemical Exposures: Dose and Time

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Responses to chemical exposures will fundamentally be determined by dose and time. Environmental pesticide exposures are of low magnitude relative to harmful levels and of short duration, even in the workplace.

Risk characterization is the latest means used in product development and regulation to evaluate and to regulate chemical technologies including pesticides. The strategy includes risk assessment, risk management, and risk communication–some persons consider these processes "Risk Assessment." The process including determination of how much and frequency of exposure formalizes safety evaluations of food residues that have occurred for over 100 years in the United States, applicator and mixer/loader exposures of the past 50 years, harvester field reentry (now "entry") during the past 30 years, and general environmental residues since the general availability of gas liquid chromatography and other advanced analytical techniques and publication of Silent Spring. Still more and more concern continues to be made of lower and lower amounts as analytical chemistry continues to contribute record of "findings" of trace analytes from diverse media–information that sometimes exercises a strong role in defining the hazardousness of many aspects of modern life, particularly public policy making.

The effectiveness of management strategies concerning reduction of current pesticide exposures and risks contrasts sharply with a listing of previously acceptable chemical exposures. General education initiatives at all levels concerning the chemical nature of the environment and the fate of chemicals in exposed persons will be required to improve risk communication. Consumers, workers, and the environment will remain the focus of Risk Assessment and default assumptions will be replaced by more defensible measures of exposure and effect. A major strength of the risk assessment process is establishment of common denominators for weighing the relationship between harmful and benign chemical exposures related to use of chemical technologies.

Multi-Component Mixtures of Endocrine Active Chemicals - Experimental Requirements and Recent Test Results

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Although the necessity of evaluating multi-component mixtures of endocrine disrupting chemicals is widely acknowledged, the prospect of approaching this topic experimentally is often dismissed because it is deemed as "too complicated". However, the last few years have seen considerable progress in this field, and this talk will give an overview of recent test results from our laboratory.

We have recorded concentration-response relationships for endocrine active chemicals in in vitro assays including the yeast estrogen screen (YES) and the E-SCREEN assay. This information was used to make predictions of the effects of multi-component mixtures composed of more than 10 components, assuming additive combination effects. It was found that the experimentally observed responses were in good agreement with the model predictions. This suggests that a large number of estrogenic chemicals are able to act together in an additive fashion.

Taken together, our test results show that estrogenic chemicals produce combination effects even when they are present at concentrations that will not yield measurable responses upon individual administration. Furthermore, sufficiently large numbers of xenoestrogens are able to modulate the effects of steroidal estrogens. This challenges the widely held view that endogenous steroidal estrogens are too potent for xenoestrogens to elicit noticeable responses, and therefore are of negligible concern.

Session 4 Human Health

Dioxin Health Effects on Humans Twentyeight Years after the "Seveso" Accident

Paolo Mocarelli

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We have followed-up with health monitoring from 1976 to 2004 thousands of people affected by the fallout of TCDD over Seveso and the nearby area which occurred on July 10, 1976. These data present advantages in that: (1) they were derived from individuals of both sexes covering all age ranges; (2) since the accident, serum samples have been kept frozen and we have been able to measure (at CDC, Atlanta, USA) the TCDD blood lipid content. We can therefore directly correlate exposure with health effects during the years. The results indicate that:

- serum TCDD levels in residents showed a very elevated exposure (up to 56000 ppt);
- chloracne was the only clinical alteration positively correlated to TCDD contamination levels, even if not completely, and with differing individual susceptibility;
- miscarriages, perinatal mortality, low birthweight or congenital malformations did not significantly increase;
- clinical monitoring of children and adults did not prove any clear association between morbidity (except chloracne) and TCDD exposure;
- laboratory results showed minimal differences between exposed (even if hugely exposed) and controls in the period of acute exposure (1976-1977) with relation to liver function tests, complement haemolytic activity, white blood cells, lymphocytes and haemoglobin. These differences were subclinical, faded and then disappeared with time.

A slight increase of leukemias, soft tissue sarcomas and rectal cancer in males has been observed after 20 years. A statistically significant dose response increased risk for breast cancer incidence was observed.

Part of the exposed people were controlled in 1992-2004 and the results showed that:

- no laboratory pathology was related to TCDD levels in both the acute and chronic phase;
- cytochrome P450 1A2 seemed to be induced after about 17 years in exposed people compared to controls as measured by the Caffein Breath Test;
- the half-life of TCDD was longer in women (about 9 years) than in men (about 7.5 years), while in children it is much shorter.

Developmental dental aberrations were associated with childhood exposure to TCDD, supporting the hypothesis that dioxins can interfere with human organogenesis.

A follow-up of about 900 women cohort showed a doubled, non significant risk for endometriosis among women with serum TCDD levels of 100 ppt or higher, but no clear dose response.

A striking skewing of sex ratio at birth (males/males+females) with excess of female ($p<0.001$) from parents exposed to TCDD has been described for the period 1977-96. This effect has been shown to be permanently related only to father exposure with the pre and puberty period being a very sensitive period. It has been recently confirmed in a dioxin induced chloracneic Austrian cohort and in exposed men in UFA, Russia..

The TCDD concentrations by which this lower sex ratio is induced in males of Seveso group are only about 20 times the estimated average concentration corrently found in human beings in industrialized countries. The human male reproductive system is demonstrated for the first time to be very sensitive to dioxin. This fact can have important public-health implications due to the different individual sensitivity in humans.

Longitudinal Studies of Children's Health

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Children are susceptible to the adverse effects of environmental exposures due to opportunities for increased contact with these risks and for unique or more persistent responses to many exposures. This has been demonstrated in studies of specific health risks, such as lead, methyl mercury, and dioxins, as well as folate deficiency. However, our understanding of environmental risk factors for children's development over the lifespan remains limited. Major advances in our understanding of preventable risks to health have been derived from large longitudinal studies of populations, which can be designed to focus on health outcomes of concern, or to examine long term outcomes associated with specific exposures, such as the CADMIBEL study in Europe or the Seychelles and Faroes studies of methyl mercury. The National Children's Study (NCS) in the US is a major response to the need for such research [website: nationalchildrensstudy.gov] The NCS is planned as a combined design, in which the major focus is on risk factors for health problems of US children as well as exposures of concern in our society. Approximately 100,000 women will be enrolled early and their children will be studied for at least 20 years. The currently identified endpoints to be studied include: low birth weight and prematurity; cerebral palsy; birth defects; autism and other developmental disabilities, asthma, diabetes, learning disabilities, obesity, abnormal sexual maturation, and mental diseases of adolescence. Exposures of concern include chemical factors like EEDs, household pesticides and pharmaceuticals; maternal and early life infectious; social factors like stable families and safe communities; and physical factors like the built environment of neighborhoods. NCS will utilize new advances in toxicogenomics for measuring outcome, exposure and susceptibility.

The first phase of the NCS provides funding to regional studies to assist in planning, development of validated measures, further hypothesis definition, and testing feasibility of data collection, identification and inclusion of special subgroups, and ensuring privacy protection of participants. Johns Hopkins is part of the Longitudinal Investigation of Fertility and the Environment (LIFE) Study, a longitudinal cohort study of births investigating impacts of chemical exposures on fertility and birth outcomes. In the Baltimore region, 288 couples from low and moderate income census tracts will be enrolled. Blood, urine and semen will be collected to measure pesticides, hormones, and biomarkers of exposure and response. The outcomes focus on fertility, miscarriages, and birth outcomes. The goal of these pilot studies is to ensure that the NCS will be a rich information resource for the world and that its findings will contribute to child health guidance, interventions, and policy for generations to come. It is anticipated that the preliminary results from the first years of the study will be available in 2008-2009, if funding is made available on schedule.

Biomonitoring: An Integral Part of Exposure Analysis

Larry L. Needham
CDC, USA

Of paramount importance in environmental public health is the assessment of the relation between human exposures to environmental chemicals and adverse health outcomes. The three primary methods for assessing human exposures are data from questionnaires, environmental measurements, and biological monitoring (biomonitoring). In this presentation, I will give an introduction to biomonitoring and examples of how biomonitoring data have been used to affect public policy and legislation. Biomonitoring data, with specific interest on chemicals that potentially may act as endocrine disruptors, from the Centers for Disease Control and Prevention's Second National Report on Human Exposure to Environmental Chemicals will also be presented. These chemicals include lead, persistent organic pollutants, phthalates, organophosphorus pesticides, and cotinine, as a marker to environmental tobacco smoke. Supplementary human data will be presented on the alkyl phenols and bisphenol A.

The data will be presented based on different age groups; both sexes, and different racial groups within the U.S. population. The data will also show how the human concentrations of many of these chemicals are decreasing over time. Finally, case studies of high exposures to some of these chemicals will be presented; for example, phthalate exposure to infants in a neonatal intensive care unit. In summary, this talk will show the importance of biomonitoring data for assessing human exposures.

DNA Methylation Profiles for Evaluation of Epigenetic Risk

Kunio Shiota

The University of Tokyo, Japan

"Epigenetics" means the study of heritable changes in gene-activity without changes in DNA sequences. In vertebrates, methylation of DNA mainly occurs at the 5'-position of cytosine in a CpG dinucleotide forming 5-methylcytosine. Methylation of DNA plays a profound role in transcriptional repression of gene expression through several mechanisms. Sequences of CpGs are not evenly distributed in the mammalian genome. They appear at a 10 to 20 times higher density in selected regions than in other regions, and regions enriched with CpGs are known as CpG islands. These CpG islands are used as landmarks to find genomic regions in bulk DNA sequences, because CpG islands are generally found in transcription units. Generally, it has been recognized that CpG islands are unmethylated in normal tissues, except the CpG islands involved in X inactivation and genomic imprinting. However, most data on DNA methylation mediated gene repression concerns TATA-less and CG-rich promoters that are associated with CpG islands. Scanning of a few thousands of islands from various cells and tissues of mouse, including ES cells and embryo revealed that CpG islands having tissue-dependently and differentially methylated region (T-DMR) were numerous and widespread in the genome. The T-DMR panel clearly indicates that DNA methylation is cell type specific. The human genome project identified 30,000-40,000 protein coding genes, and there are approximately 29,000 CpG islands. There are 30,000 genes and 15,000 CpG islands in the mouse genome. Tissue-specific promoters revealed that 50% of CpG islands are linked to tissue-specific genes. The remaining tissue-specific promoters do not associate with CpG islands. A single fertilized egg gives rise to a complex multi-cellular organism consisting of at least 200 differentiated cell types. Most cells differentiate without changes in DNA sequence through activation of a particular set of genes and inactivation of others. The molecular basis for the memory for activated or inactivated gene sets, which is inherited to the cells' next generations, is critical for differentiation and development of multicellular organisms. Thus, formation of DNA methylation pattern underlies mammalian development, and epigenetic errors cause other diseases. Changes in heritable DNA methylation which alter phenotype are referred to as epimutagen. Now, evaluation of mutagens as well as epimutagens are needed in the environmental-pathology and -toxicology.

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Session 5 Future Research Directions

Evaluation of Chemicals for Endocrine Disruption: Future Research Needs

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How any given organ appears to respond to a hormone can depend greatly on which assays are conducted. Also, different organs can respond differently to the same hormone. And animals and individual organs can respond differently to the same hormone at different stages of development. Consequently, hormonal responses are assay-, organ-, and age-dependent.

None of these complexities would present problems for the assessment of endocrine disruptors if the efficacy and potency of any given chemical were the same from one assay, organ, and age to another. If that were the case, one would simply compare the efficacy and potency of a chemical with that of the appropriate prototype hormone under any convenient set of experimental conditions. But the endocrine system is not that simple. Not only can the same sorts of assay-, organ-, and age-dependent differences seen with hormones be seen in response to endocrine disruptors, but the *pattern* of responses can vary greatly from one chemical to another. In other words, efficacies and relative potencies for endocrine disruptors can be strongly assay-, organ-, and age-dependent. Many chemicals are selective receptor modulators, and some chemicals even have opposite endocrine effects on different organs. Consequently, no single measurement is capable of assessing the estrogenicity or anti-androgenicity or thyroid hormone agonist activity, etc., of a chemical. Instead, multiple measurements have to be made for each chemical, even within the same class of activity (e.g., estrogenicity), in order to determine the most sensitive response(s) of toxicological significance.

Given the complexities of the endocrine system and of the biological processes that it regulates, is there any way to evaluate endocrine disruption without spending large amounts of money per chemical on each of many thousands of chemicals? It appears that there is no alternative but to conduct expensive whole-animal tests on dozens of prototype chemicals, presumably as an international undertaking. These tests would have to include continuous, multi-generation exposure and multiple sensitive functional measurements. The goal would be to identify the most sensitive *in vivo* responses of toxicological significance for each class of endocrine disruptor. This testing would also create the databases needed to determine the extent to which any of the inexpensive screens and tests correctly predict the adverse endocrine responses that we are actually concerned about. Because no such database now exists for any class of endocrine effects, screens and short-term tests cannot yet be validated. Governments cannot regulate endocrine disruptors until these databases are created.

If the comprehensive whole-animal tests on prototype chemicals incorporate genomics, proteomics, and metabonomics, and if enough prototypes are studied, it may be possible to identify surrogate measurements for the key adverse responses. If this proves to be the case, or if a combination of screens and short-term tests accurately predict the most sensitive responses of toxicological concern, there would be no need to spend vast sums of money comprehensively testing thousands of chemicals. Instead, relatively inexpensive tests that accurately predict the results of the expensive and comprehensive whole-animal tests could be used to determine how large or small the endocrine disruption problem really is and to identify which chemicals cause it.

Effects of Endocrine Disruptors on Behavioral Developments of the Brain and Neurodevelopmental Disorders ---- PCBs and Some Agricultural Chemicals Disrupt Gene Expressions, Suggesting a Causal Factor of LD, ADHD and Autism

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In US and Japan, there is an increasing number of children with learning disorder (LD), attention deficit hyperactivity disorder (ADHD) and autism. Environmental (both chemical and social) and genetic factors interact and determine human cognitive functions and behaviors, both normal ones and their disorders, through synaptogenesis in developing brain and later through plastic changes of the formed neural circuits activities, both of which are subserved by cascades of gene expressions in the brain.

We have established quantitative assay systems both in vitro and in vivo to detect effects of environmental endocrine disruptors (EEDs) on the development of brain: for molecular level (gene expressions); reporter assays, high through-put assays, for cell level; synaptogenesis and dendrites extension assays using cultured neurons and for behavioral level; computer-analyzed open field test using rodents; "Finger-maze" learning test, eye contact test, social behaviors and mother infant interactions using monkeys

Thyroid hormone-dependent gene expressions are essential for the functional development of the brain. By reporter gene assays, they are inhibited by the exposure of low doses (pM orders) of PCB and hydroxy PCB (metabolites of PCBs in the brain) (JBC,279:18195,2004). Molecular mechanism of low dose effects of PCBs and other EED has been proposed as "Single DNA target" hypothesis (Kuroda, Y., Environ. Sci. 10:23, 2003). Low doses of hydroxy PCBs also inhibited dendrites extension of Purkinje cells and synaptogenesis in culture which is thyroid hormone-dependent (Develop. Brain Res,137:55,2002).Significant correlation between total PCBs levels in the blood of mother monkeys and defects in the performance of their offsprings in the "finger-maze" learning test is consistent with the deficits of intellectual abilities (5 points down of their IQ scores) of children born to the mother who had perinatal exposure to PCBs in Yu-Cheng incident.

Learning, memory and other epigenetic higher functions of the brain are carried out by neuronal activity-dependent gene expressions in the brain. Depolarization-induced gene expressions are inhibited by DDT, pyrethroides insecticides and DRS. When 3 agents were exposed together, the result was additive (JPET, 295:1175,2000). Excitatory neurotransmitter glutamate-induced gene expressions were over-stimulated by glufosinate (organophosphate glutamate compound), commonly used for gene-modified crops. The data are consistent with the evidence that glufosinate induced excitement and aggressive behaviors to killing in offspring born to mother exposed to the herbicide.

LD, ADHD, high functional autism and Aspergar syndrome children show heterogeneity and co-morbidity, having complex combination of various symptoms.

Considering the continuous complex contamination of environmental chemicals such as PCBs in human body and brain, EEDs and other environmental chemicals are one of the possible causal factors of neurodevelopmental disorders. Thyroid hormone-dependent and neuronal activity-dependent gene expressions in the fetal and newborn brain, where most synaptogenesis and circuits formation occur, can be disrupted by spatio-temporal exposure of environmental chemicals. They cause various patterns of deficits in neural circuits of any functional areas in the brain, resulting the heterogeneity and co-morbidity of symptoms in disordered children.

Ecotoxicogenomics & the Assessment of Endocrine Disrupters in Aquatic Organisms: Future Opportunities and Validation Needs

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In recent decades, regulatory ecotoxicology has often sought to establish which chemicals cause damage to ecosystems through the use of non-mechanistic tests. The endocrine disrupters issue arguably marks a historical step change in bringing mechanistic biomarkers (such as vitellogenin) into the regulatory test guideline arena, with associated practical challenges in biomarker validation. As we move into a new century, however, rapid progress in the field of toxicogenomics is now beginning to provide tools that can assist our understanding of the mechanisms via which chemicals cause endocrine disruption. More broadly, the term 'ecotoxicogenomics' has been proposed to describe the study of gene and protein expression in wildlife in response to environmental toxicant exposures (Snape et al., 2004). There are several examples of how gene expression assays are being applied in aquatic invertebrates and fish exposed to endocrine disrupters. However, the sheer number of ecotoxicology species available potentially risks spreading research resources too thinly and hence there is a need for an international ecotoxicogenomics network to help prioritise species of interest. For aquatic ecotoxicogenomics to fulfil its potential, it is proposed that global efforts prioritise 'omic profiling of selected plant (Lemna minor), invertebrate (Daphnia magna) and fish (Danio rerio, Oryzias latipes and Pimephales promelas) species. In the long term, this will help strengths and weaknesses of ecotoxicogenomics - which promises to be a significant new source of biomarkers for use as hazard alerts. The scientific community needs to focus on this question today with a view to the decade ahead, for in the words of the Roman philosopher Seneca, "If one does not know to which port one is sailing, no wind is favourable".

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Further Important Aspects of Epidemiological Studies for Detecting Subtle Effects in Children Exposed to Endocrine Disrupting Chemicals during Gestational Periods

Reiko Kishi

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Based on the animal experiments, the most sensitive target of EDCs seemed to be fetus. In utero exposure to EDCs may cause adverse effects on some congenital malformations, such as hypospadias or cryptorchidism, or changes of neurobehavioural function, thyroid hormone level, changes of allergic diseases in infants. However, so far there are only a limited number of epidemiological evidences to explain the causal relationships between health outcome and EDCs. In paticular, a few well-designed epidemiological reports are available concerning on the low background level of exposure.

For instance, ICBDMS indicated possible increases of congenital malformations in some countries, e.g. USA or Denmark, but not in Britain nor in Finland in these two decades. In Japan, our data based on urological surgery statistics which include more minor hypospadias malformation did not indicated such increase, which means large differences between countries and ethnicity. Prenatal exposure to back ground level of PCBs in Rotterdam was associated with delayed motor development until 42 months old, but the association was disappeared at 6 to 7 years old (Vreugdenhil et al., 2002). In North Carolina study, prenatal exposure to back ground level of polychlorinated biphenyls was associated with delayed motor development until 24 months old, but the association was disappeared at 3 to 5 years old (Rogan and Gladen, 1991). On the other hand, in multi-center study of USA, there was no association between prenatal exposure to back ground level of polychlorinated biphenyls and mental and psychomotor development at 8 months old (Daniels et al., 2003).

Higher levels in human milk correlated significantly with lower plasma free thyroxine (T3) and total T3 levels in the second week after birth (Koopman-Esseboom, 2004). Estimated total intakes of PCDD, PCDF, and Coplanar-PCB in toxic equivalent quantity (TEQ) from the breast milk significantly and negatively correlated with the levels T3 and thyroxine (T4) in the blood of 34 breast-fed babies in Japan (Nagayama, 1998). Cord blood IgE may be associated PCB exposure (Reichrtova et al., 1999). But Weisglas-Kuperus et al. reported that a higher prenatal PCB exposure was associated with less shortness of breath with wheeze, so they speculated that prenatal PCB exposure might be associated with a lower prevalence of allergic diseases (2004). Thus, influences of PCBs and dioxin on malformation, neurological and intellectual function, hormone level, and allergy diseases in infants and young children are not conclusive, and there has been few data about their relationships in Japan.

Recently we started two prospective cohorts in Hokkaido Prefecture, Japan, One of which is for birth defects monitoring systems, and the other is infant developmental study. In both studies, gene polymorphisms of xenobiotic-metabolizing enzymes are investigated to elucidate individual susceptibility to background levels of exposure on fetuses. Analysis of microarrays for SNPs is also applied to detect the high-risk groups according to individual genetic factors. The main goal is to understand the ways in which the chemical and social environment interact, over time, with the genetic inheritance to affect children's health, behaviour and development

In this conference, I will discuss recent important issues on epidemiological studies, especially focused on methodological aspects, indicating our studies of hypospadias or cryptorchidism. In addition, some results on thyroid hormone level in the pregnant women, neurobehavioral tests, and cord serum IgE level of their infants, will be shown presenting the relationship between serum PCBs and dioxin levels, fish consumption, smoking habit, and gene polymorphisms of xenobiotic-metabolizing enzymes in pregnant women.

Session 6 Risk Communication

Effective Risk Communication: Its Philosophy and Technique

Tomio Kinoshita
Koshien University, Japan

Society today, feeling itself exposed to a variety of risks, has increasingly demanded effective risk communication. Risks related to environmental endocrine disrupters is one such urgent example.

This article includes ①the psychological nature of risk on environmental endocrine disrupters, ②philosophy and value system underlying risk communication, ③the principles of risk communication, ④variables which influence the effects of risk communication, ⑤the paradigm of risk communication and its empirical data, ⑥organizational climate (or leadership of top managers)as a factor in successful risk communication, and ⑦some poor examples and some good examples of risk communication in Japan.

セッション6 リスクコミュニケーション

リスクコミュニケーションの思想と技術

木下 冨雄
甲子園大学

様々なリスクにさらされている今日の社会では、効果的なリスクコミュニケーションがますます必要となってきた。環境中の内分泌攪乱物質に関するリスクコミュニケーションはまさにその一つの例である。

本講演では、①環境中の内分泌攪乱物質の心理的特質、②リスクコミュニケーションの基礎にある思想と価値システム、③リスクコミュニケーションの基本原則、④リスクコミュニケーションの効果に影響を及ぼす要因、⑤リスクコミュニケーションのパラダイムとその実証データ、⑥リスクコミュニケーションが成功するための組織風土（あるいは組織トップのリーダーシップ）、⑦わが国におけるリスクコミュニケーションの失敗例と成功例、などについて述べる。

Risk Perception of Endocrine Disrupting Chemicals

Toshiko Kikkawa
Keio University, Japan

This presentation reports on the results of a survey we conducted on endocrine disrupters. A total of 2,500 people in the metropolitan Tokyo area and the Kansai area participated in the survey. The main results were as follows:

1) While approximately 2/3 of the respondents had never heard of the technical term "endocrine disrupting chemicals," approximately 90% of them knew of the term "environmental hormone" instead, which is not scientifically correct. 2) Whereas the need for information was potentially high, scientifically incorrect knowledge so-called "laypersons' knowledge") was very common. 3) More than 70% of the respondents did not know that the relation between endocrine disrupters and human health damage has not yet been scientifically proven. 4) The result of a latent structure analysis revealed that there were some significant links between attitude and behavior concerning endocrine disrupters. 5) People who have more frequent contact with the mass media were found to be more risk-aversive.

内分泌攪乱化学物質に対するリスク認知

吉川　肇子
慶應義塾大学

筆者らが内分泌攪乱化学物質についての国民意識調査の結果を報告する。調査対象者は、首都圏および近畿圏のうち、20歳～69歳の一般男女2500名であった。主要な結果として1. 内分泌攪乱物質（調査票では「内分泌かく乱物質」と表記という用語そのものを聞いたことがない回答者が約2／3ある一方で、俗称である「環境ホルモン」という用語は約9割が「知っている」と回答していた。2. 情報に対するニーズは潜在的に高かったが、一方で科学的に正確ではない知識（いわゆる「しろうと知識」）はかなり知られていた。3. 内分泌攪乱物質とヒトの健康障害との関連について、科学的には未証明であるという事実を知らなかった回答者が7割強あった。4. 知識と態度間の関連を分析したところ、共通して有意に認められた関連性は、「証拠を重視する態度→マスメディア接触量→ベネフィット認知→リスク回避行動」、「証拠を重視する態度→マスメディア接触量→リスク認知→リスク回避行動」、「探究心→求めている情報→行政への要望→リスク回避行動」であった。5. マスメディア接触量が他の認知要因に影響を及ぼし、その結果、人のリスク回避行動を規定していることがわかった。

What and Why We Lay Persons Don't Understand, and How You Experts Misjudge Them

Hiroo Yamagata
Reviewer, Translator, Japan

Discussions on risk are necessarily not clear-cut. Especially in the environmental issues, the risk at stakes are far below the level that people even feel worthy of thinking about, and their effects often become apparent only after a century or so, as is in the case of global warming. In order to make it into a political agenda, their negative effects are often exaggerated, which in turn leads to an overly emotional over-response that does not correspond to the actual danger, as seen in the case of dioxin, synthetic estrogens and the recent BSE scare.

This is caused by the innate recognition pattern of human beings, coupled with the mass media that finds scare stories more "newsworthy," as well as various organizations who find it in their interest to oversell the danger (with good intent). Also, the pattern of Greedy Corporations with Government VS the People, which does not apply anymore, is still being exploited, only to confuse the matter. The presentation points out several ideas and methods that are often the sources of major misunderstandings, and raises cautions for both the senders and receivers of various environmental information, as well as propose better training and education to supplement the weaknesses inherent in the human nature, such as the understanding of probabilities, in order to improve the risk communication in the environmental issues.

一般人の誤解と専門家のかんちがい：環境問題の何がなぜわかりにくいのか

山形　浩生
評論家・翻訳家

リスクの議論はどうしてもあいまいにならざるを得ない。特に環境関連の話題では、扱われているリスクは日常生活で人々が完全に無視する水準をはるかに下回るし、またその影響も、地球温暖化などでは100年以上先にやっと出る水準でしかない。それを政治的な課題として採りあげようとすれば、マイナス面を誇張せざるを得ないが、これはダイオキシンや環境ホルモン問題、BSE問題で見られるような、実際の危険性とまるでかけ離れた過敏な感情的反応を引きおこすことになる。

これには、人間の持つ基本的な認識方式の限界とともに、扇情的でなければニュース価値が低いとするマスメディア、また問題を煽ることで利益を得る団体による（しばしば善意の）歪曲なども貢献している。さらに1970年代の公害問題で有効だった、政府+企業vs市民団体、といった図式が成立しなくなっているのに、未だにこの図式が多用され、話をややこしくする。情報の送り手や受け手双方が注意すべき各種の歪曲や誤解の種となる概念、そして基礎的な確率概念についての教育などを、人間の持つ生得的な認識の限界を補う形で強化することが、もっとよい環境問題理解には必要である。

Risk Communication of Endocrine Disrupting Chemicals Produced by Industries Among Consumers, Producers, Administrators and Scientists

Saburo Matsui

Kyoto University, Japan

Environmental endocrine disrupting researches for the last five years in Japan as well as other countries can provide us many new insights into toxic mechanisms of them with human and animals at the levels of body, organs and DNA interacting molecules. The advanced technology of DNA micro-array with human genes revealed how endocrine disrupting chemicals up-regulate and down-regulate 30,000 human genes. This new technology guides a completely new horizon of life science to understand complex chemical interactions with enzymes mobilized by genes. Human cells of 60 trillion ($6x10^{12}$) beautifully coordinate and sustain our body. Each cell is driven its function by coordinating the extremely complex networking of 30,000 genes. Toxicity of TCDD, for example, is interpreted in one way that the chemical is not oxidized nor reduced inside the cell, but exert its toxicity by over reacting with Aryl-hydrocarbon Receptors that mobilize many Cytochrome P450 genes of oxidation enzymes including 1A1,1A2, 19A1 and others. Those over produced P450 enzymes disturb the balance of oxidation and reduction of other numberless chemicals in side the cell, which may lead unnecessary oxidation of DNA basses in the forms of OH- adduct such as 8-oxo-dG, 5-OH-dC, and 2-OH-dA,etc, and which may further lead excess mutations of genes and at worst carcinogenesis of the cell. The target genes are in number of 30 hundred million pair bases ($30 x10^8$) per cell. The great number does not allow us safety relief that there is a plenty chance of escaping from getting cancer disease. Our body is constantly accepting those mutations with 60 trillion cells for life time. Japanese population dies at one forth by cancer disease.

TCDD is difficult to escape from a cell. The half life of TCDD of human body is estimated to be about 7.5 years. It escapes daily from a human body through feces and skin secretion, not urine. A pregnant mother transfers it into her fetus so that after birth, her body contamination level is drastically improved. Environmental endocrine disrupting chemicals raised many questions that require more research in fundamental science of cell biology at DNA molecular levels with simultaneously further understanding of the contamination levels of water and land ecosystems. Major routes of hazardous chemicals input to animals are food chains. We, Japanese, heavily rely on our protein on fishes while many other peoples on land mammals. Baltic Sea, Great Lakes are heavily contaminated with Dioxins and PCBs, etc, so that Governments warn that pregnant mothers do not eat fishes caught from those waters more than once a month. This warning brings us an important precaution that we must not contaminate Pacific Ocean as well as Japan Sea and around the waters for our descendants.

How to communicate the risk with endocrine disrupting chemicals and other hazardous chemicals produced by industries. The primary responsibility definitely goes to producers of industries. They know how new chemicals are toxic and harmful in the environment. Producers should provide information of environmental toxicity of their new chemicals to public. However, environmental scientists concern very much that rapid increase in new chemicals in the market may produce so called "the complex effects" on human health. It is a wise approach to take the consideration of the quota control of hazardous chemicals discharged in the environment. Evolution of human cannot meet to so many exotic chemicals such as TCDD, PCBs and possibly Fullerene and Nano-tubes. The government role is not protecting industry from consumer criticism, rather facilitates good quality of toxicity information of new chemicals from industry to public. Consumer needs to build up more knowledge of environmental toxicity as well as their basic knowledge of modern health. The risk communication aims gaining and building "environmental trust" among consumers, producers, administrators and environmental scientists.

消費者、製造業者、行政、科学者の間で、産業によって製造された内分泌撹乱物質のリスクコミュニケーション

松井　三郎
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この5年間、日本や他の国で進められた内分泌撹乱物質の研究は、ヒトと動物の身体、臓器、ＤＮＡレベルで毒性機構を理解する新しい知見を生み出した。ＤＮＡマイクロアレイ技術は、ヒト遺伝子3万種が活性化、抑制化される状態を観測可能にした。この技術により遺伝子が動き酵素が生成され、複雑な化学反応が進行する生命現象を、理解する全く新しい科学領域が切り開かれた。60兆個の細胞が見事に調和してヒトの生命を維持している。一つ一つの細胞は、3万個の遺伝子の極めて複雑な、ネットワークにより動かされている。例えば、TCDDの毒性機構は次のような説明も可能である。すなわち、細胞内でAh受容体と結合しても酸化、還元の反応を受けず、Ah受容体と結合し離れまた結合する繰り返しの過程でチトクローム450酵素群（1A1,1A2, 19A1等）を過剰に動かし、DNA塩基に酸化的にOH付加体―8-oxo-dG, 5-OH-dC, and 2-OH-dA等を生成する。その結果、遺伝子損傷となりその修復が完全でないことから、突然変異、発癌にいたる道である。しかし、標的となる遺伝子塩基対は、1個の細胞に30億個存在するから少々の傷がついてもすぐには発癌しないという安心はできない。人体の60兆個の細胞は、生涯、恒常的に遺伝子の突然変異にさらされている。日本人口の4分の1は癌による死亡である。

TCDDは体内に入ると排出しない。ヒトで体内半減期は7.5年と推定されている。体外へは、皮膚から皮脂と一緒に、また糞と一緒に排出され、尿からは排出されない。しかし、妊産婦は、胎児に移行させ、出産により自身のTCDDは大幅に減少する。内分泌撹乱物質問題は、水、生態系の環境汚染の研究と同時に、生命科学のDNAレベルにおける基本的疑問を解明することを必要としている。動物に侵入する有害物質の主要経路は、食物である。我々日本民族は、蛋白質を魚類に依存し、他の多くの国の人口は陸上動物に依存している。バルト海、五大湖は、ダイオキシン、PCB他の物質で、ひどく汚染されていることから周辺国政府は、妊婦に対して汚染魚を月一回以上摂取しないように警告している。このことは我々日本人にたいして重要な予防的対応をすることを警告している。すなわち、周辺海域、日本海だけでなく太平洋を子孫のために汚染してはならない。

化学産業によって製造される有害化学物質、内分泌撹乱物質のリスクコミュニケーションをどのように進めるか？主たる責任は製造業者にある。製造業者は新規化学物質が環境に対してどれだけ有害か知っている。製造業者は新規物質の毒性に関する情報を公開しなければならない。しかし環境科学者は、急速に市場に投入される新規化学物質の数が増加することに懸念を抱いている。特に無数の化学物質の「複合影響」が、わからない状況から、環境に放出される有害化学物質の「総量規制」と新規物質の「割り当て規制」が必要と考える。人間の進化がゆっくり進行するが、TCDD, PCBsなど無数の新規化学物質に適応することは困難と予測される。新規化学物質の中に、ナノテクノロジー材料として注目されているフラーレンや、ナノチューブも含まれている。

政府の役割は製造業者が消費者から批判うけることを庇うのではなく、新規化学物質の毒性に関する上質の情報を公開促進することである。消費者は、健康に関する最新の知識と化学物質の環境毒性を理解する知識を強化することが求められている。リスクコミュニケーションの目的は、消費者、製造業者、行政と環境科学者の間で、「環境信頼形成」を行うことである。

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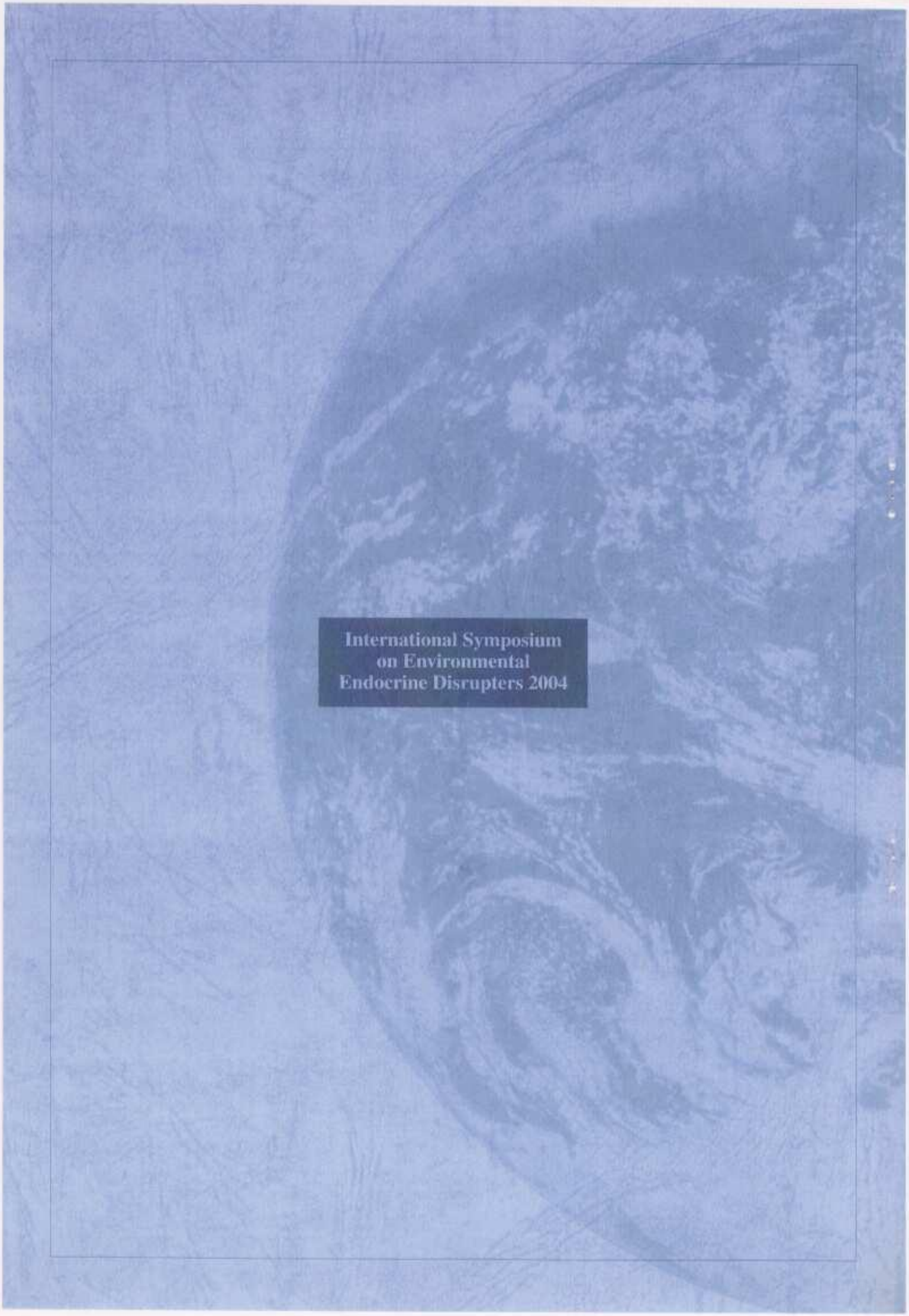
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