- EURISKED studies the interaction between endocrine disruptors with estrogenic actions; and
- FIRE: aims at an improved, integrated risk assessment of brominated flame retardants for human health and wildlife.

Together, these projects represent more than 60 research laboratories in Europe, with a total budget of more than 20 million Euros. Research on endocrine disruptors is believed to cross traditional borders between human health and environmental research and include themes important to integrated risk assessment such as combined effects, human and non-human receptors, and multi-pathway exposure.

In 2003, a further research call on integrated risk assessment resulted in two projects, NoMiracle and ERApharm, with 54 partners and a total budget of 12.8 million Euros. NOMIRACLE (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe, www.dmu.dk/International/Environment + and + society/ NOMIRACLE/), will develop methodological systems to analyse interactions between environment and health, and integrated risk assessments methods for the evaluation of cumulative effects, interactions between stressors and their influence on human health. ERApharm (Environmental Risk Assessment of pharmaceuticals, http://www.erapharm.org/summary.html) aims to advance existing knowledge and methods for evaluating potential risks, which human and veterinary pharmaceuticals pose to the environment.

In addition to opportunities focused specifically on chemicals, increasing international attention is focusing on problems associated with cyanobacterial blooms as they affect drinking water supplies, agricultural production, recreational opportunities and other ecosystem services, and the condition of aquatic and terrestrial communities. An integrated approach to risk assessment of these blooms was considered at the recent International Symposium of Cyanobacterial Harmful Algal Blooms (Orme-Zavaleta and Munns, submitted). The approach outlined during the symposium considered the direct and indirect effects of cyanotoxins as well as effects that can result from increased algal biomass and other bloom-associated stressors. It also considered socioeconomic risks resulting from loss of ecosystem services and other insults to human well-being. Although not yet finalized at the time of this writing, the symposium report will recommend a number of research directions that will not only support integrated assessments of risks of cyanobacterial blooms, but also development and acceptance of integrated risk assessment as a decision-support methodology.

ISSUES OF DEVELOPMENT AND IMPLEMENTATION

The impediments to the development and implementation of integrated risk assessment are, in general, not regulatory in nature. In most nations, the laws that control pollution to assure the quality of air, land, and water call for protecting both human health and the environment which may imply that assessments take on a holistic approach. Rather, the impediments are institutional and technical.

Institutional Impediments

Some new governmental entities such as the EU and the Republic of South Africa are availing themselves of the opportunity to base their new environmental management on integrated approaches. However, most governments, such as those of the United States, Canada, and Japan, are implementing decades-old laws, using established regulations, in well-entrenched institutional structures. Although the laws might have been enforced in an integrated manner and there is some impetus toward that direction in various assessment activities, they were not. Instead, risks to human health and to nonhuman populations and ecosystems have been assessed separately by distinct groups within regulatory organizations. Over time, they have developed separate approaches and methods that have been incorporated into guidance documents.

Failure to integrate assessments is most obvious in the development of different approaches to the analysis of exposure-response relationships. For example, in the U.S. human health benchmarks such as reference doses are estimated by applying factors of 10 to No Observed Adverse Effects Levels to account for extrapolations between species and between typical humans and sensitive subpopulations and for uncertainties such as from minimal data sets. Quantitative uncertainty analysis of human exposure-response benchmarks is currently precluded by policy. In contrast, quantitative uncertainty analysis may be applied to ecological exposure-response analyses along with probabilistic extrapolation models such as species sensitivity distributions (USEPA 2004). Similarly, toxicity testing of effluents and ambient media is commonly used in ecological risk assessments but not in human health assessments. These discrepancies in assessment methods illustrate the degree of separation of human health and ecological risk assessment in practice and suggest that integrated assessment will require overcoming the policies that create technical barriers.

The opportunities for integration are more obvious in the modeling of chemical transport, fate, and exposure, and the use of common transport and fate models for human health and ecological assessments is common. However, even here institutional barriers operate. For example, the accumulation of chemicals by fish and shellfish has recently been addressed by USEPA guidance for water quality criteria to protect human health (USEPA 1998). Clearly, this is also an important issue for ecological risk assessment. It would have required little additional effort to address issues related to wildlife (*e.g.*, consumption of whole fish versus filets) and publish integrated guidance.

The opportunities for integration could be increased by one important change in risk assessment practices, the weighing of multiple lines of evidence to characterize exposure, response and risk. For example, in the United States toxicological benchmarks for human health are based on a single critical study. That critical study is usually a rodent chronic toxicity test. If, rather than a single critical study, all relevant toxicological data may be used, it would be possible to use data from nonstandard mammalian tests as well as tests of birds and fish. The test data could be interpreted in the light of observations of ecological effects in the field such as deformed piscivorous birds and diseased marine mammals. By weighing the evidence from conventional mammalian toxicology, ecotoxicology, human epidemiology, and eco-epidemiology, risk assessors could better characterize mechanisms of action and

the forms of the relationships of exposures to responses. However, the policy of using a single critical study inhibits that weighing of the entire body of human health and ecological data.

Finally, the institutional tradition of considering only direct effects on human health reduces the opportunities for integration. Although ecological risk assessments consider indirect effects of chemicals including loss of food resources and habitat structure, human health risk assessors do not consider how human health and well-being are affected by damage to the environment. Indirect effects on health have been little studied but could include reduced consumption of wholesome foods such as fish due to contamination, loss of the health benefits of outdoor recreation, and the health effects of stress due to loss of livelihood when resources are destroyed or stress due to perceptions of inhabiting a degraded environment. Even when indirect health effects cannot be demonstrated, reduced environmental quality can result in reduced quality of life. Finally, as ecosystems are degraded, services of nature such as water purification and pollination are lost, resulting in economic costs. None of these effects of chemicals on humans are routinely assessed, because they are not institutionally recognized as risks to humans. If they were, assessments of those risks to human health, well-being and quality of life would necessarily be integrated with ecological risk assessments.

Technical Impediments

Much of the interest in integrated risk assessment of chemicals is associated with the possibility of using the increasing knowledge of toxicokinetics and toxicodynamics to assess effects on various species using a common mechanistic framework. For example, estrogenicity, cholinesterase inhibition, and the "dioxin-like" toxicity of Ah receptor agonists are toxicodynamic mechanisms common to all vertebrates. Similarly, except for the lung/gill dichotomy, the basic routes of toxicokinetics are common to all vertebrates. However, case studies performed by the WHO/IPCS integrated risk assessment program have shown that the benefits of this approach are constrained by the types of data and models that are currently available. That is, knowledge of shared mechanisms will benefit mechanistic assessments more than the current risk assessment approaches that treat effects phenomenologically. Greater benefits will come as the growth of mechanistic knowledge and testing methods leads to new cellular and molecular tests, molecular modeling, and organism simulation modeling. Increasing knowledge of the genomics, proteomics and metabonomics of a wider range of species holds out the promise of being able to address effects by modeling when testing is not practical. As a result, it should become practical to assess risks to taxa such as cetaceans, amphibians, and reptiles that are not now routinely considered. The primary impediment to realizing this vision is the tremendous complexity of the necessary assessment models and their data requirements. However, because of the importance of these techniques to biomedical science, the necessary molecular methods and computational tools are developing rapidly (Waters *et al.* 2003).

There are dangers in attempting to implement this vision of integrated risk assessment. The greatest danger is that ecological risk assessments will become too focused on the effects that other species have in common with humans and will

miss biological eccentricities. Egg-shell thinning by DDE in birds, deformities in molluscs exposed to tributyltin, and inhibition of the mating pheromones of newts by endocrine disruptors are some of the sorts of responses that would be missed by all but the most sophisticated imaginable toxicodynamic models. This danger could become an impediment to the development of integrated risk assessment, if it is perceived that integrated assessment misses important effects on non-mammalian species. However, the current regulatory test sets also miss many effects. The development of integrated mechanistic risk assessment will make it even more apparent that eco-epidemiological monitoring is needed, along with epidemiological monitoring of public health, to reveal unanticipated effects. Integration of available knowledge in various assessments may give deeper insight and help understanding real situations as shown in examples in the section on "Benefits of Integration" for complex exposure situations.

Another danger is that integrated risk assessment will become too focused on risks to vertebrate organisms and neglect other ecological endpoints. This is already occurring in the sense that toxicity testing is disproportionately performed with vertebrates. This is problematical from the ecological point of view given the much great importance of invertebrates, plants, and microbes to the functioning of the biosphere. If risk assessment becomes fully integrated, there could be an even greater temptation to neglect mechanisms that are not shared with humans and the species possessing those mechanisms.

RECOMMENDATIONS FOR CONTINUED DEVELOPMENT AND ACCEPTANCE OF IRA

To summarize, the strengths of IRA are:

- Risk-based decision-making will be informed of all risks that are potentially significant,
- IRA may predict and diagnose previously unexpected risks,
- Assessment efficiency will increase with regard to data collection, methodology and decision-making,
- Cost effectiveness will increase in view of shared resources,
- Assessment results will be more coherent in view of shared methodology and characterization of exposure, hazards and risks, and
- Assessment uncertainty will decrease by confirmation of mechanisms of action and increased knowledge on toxicokinetics and toxicodynamics.

However, a number of serious weaknesses can also be identified, not so much in the approach *per se*, but rather in the demonstration of its benefits and in organizational backing:

- Although several cases have been studied to demonstrate the benefits of IRA, none of them have demonstrated convincingly that this approach will be efficient and cost effective.
- These case studies also revealed that an increased quality of the assessment seems likely, but hard to prove.

- Although many regulations call for protection of both human health and the environment, scientifically and institutionally these areas often have developed independently.
- The emphasis on direct effects on human health reduces the opportunities for integration.
- The knowledge of shared mechanisms, testing methods and integrated testing strategies still has to evolve to really appreciate the benefits of IRA.

It is clear that further demonstrations of the scientific, economic and regulatory benefits of the IRA approach are needed. Our analysis of opportunities for the promotion of IRA shows that, apart from scientific reasons, societal and political pressures require increased efficiency in risk assessment as well as moving away from vertebrate testing. This necessitates integration of *in silico*, *in vitro*, and *in vivo* methods across species. As risk assessment is becoming more mechanistic and molecular there may be new opportunities to create an integrated approach based on common mechanisms and a common systems-biological approach. This development will automatically provide the examples asked for, which subsequently have to be analyzed for economic and regulatory benefits.

ACKNOWLEDGMENTS

The contribution of all members of the IPCS Planning Group on Approaches to Integrated Risk Assessment to the project is gratefully acknowledged. The authors also thank the reviewers for their comments. This work was partly carried out with budget provided by The Netherlands' Directorate-General of Environmental Protection (project no. M/601200).

LIST OF ABBREVIATIONS

EC (European Commission), EPA (U.S. Environmental Protection Agency), ERF (Emergency Response Function), EU (European Union), FAO (Food and Agricultural Organization), IPCS (International Programme on Chemical Safety), OECD (Organization for Economic Cooperation and Development), POP (Persistent Organic Pollutant), REACH (Registration, Evaluation, Authorisation and restriction of Chemicals), SIDS (OECD Screening Information Data Set), WHO (World Health Organisation).

REFERENCES

Bontje D, Hermens J, Vermeire T, *et al.* 2005. Integrated risk assessment: nonylphenol case study. WHO/IPCS/IRA/12/04.World Health Organization/International Programme on Chemical Safety, Geneva, Switzerland

Bradbury SP, Feijtel TCJ, and van Leeuwen CJ. 2004. Meeting the scientific needs of ecological risk assessment in a regulatory context. Environ Sci Technol, December 1, 463A–70A

Briggs J. 2003. Human health and environmental risk assessment: the need for a more harmonised approach. Chemosphere 52:1347–51

EC (European Commission). 2003a. Technical Guidance Document on Risk Assessment (TGD) in support of Commission Directive 93/67/EEC, Commission Regulation (EC) No 1488/94 and Directive 98/8/EC. European Chemicals Bureau, Ispra, Italy

EC. 2003b. Communication from the Commission to the Council, the European Parliament and the European Economic and Social Committee—A European Environment and Health Strategy. COM/2003/0338. Commission of the European Communities, Brussels, Belgium

EC. 2004. Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee—"The European Environment and Health Action Plan 2004". COM(2004)416. Commission of the European Communities. Available at http://europa.eu.int/comm/environment/health/index_en.htm, Brussels, Belgium

EC. 2006. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency and amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC and 2000/21/EC. Commission of the European Communities, Brussels, Belgium. Off. J. Eur. Union L 396/1-856.

Euling SY and Sonawane BR. 2005. A Cross-Species Mode of Action Information Assessment: A Case Study of Bisphenol A. EPA/600/R-05/044F. US Environmental Protection Agency, Washington, DC, USA

Hansen L, Hedtke SF, and Munns WR Jr. 2003. Integrated human and ecological risk assessment: a case study of ultraviolet radiation effects on amphibians, coral, humans, and oceanic primary productivity. Human Ecol Risk Assess 9:359–77

Höfer T, Gerner I, Gundert-Remy U, *et al.* 2004. Animal testing and alternative approaches for the human health risk assessment under the proposed new European chemicals regulation. Arch Toxicol 78:549–64

IPCS (International Program on Chemical Safety). 1979. DDT and its Derivatives. Environmental Health Criteria 9. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

IPCS. 1989. DDT and its Derivatives—Environmental Aspects. Environmental Health Criteria 83. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

MOE (Ministry of Environment). 2003. Chemicals in the Environment, Report of the Environmental Survey and Wildlife Monitoring of Chemicals in FY2001. Environmental Health Department, Ministry of the Environment, Japan, March 2003

Munns WR Jr, Suter GW II, Damstra T, *et al.* 2003. Integrated risk assessment—Results of an international workshop. Hum Ecol Risk Assess 9:379–86

Orme-Zavaleta J and Munns WR Jr. Integrating human and ecological risk assessment for the cyanobacterial harmful algal bloom problem. Adv Exper Med Biol (in press)

Ross P and Birnbaum L. 2003. Integrated human and ecological risk assessment: a case study of persistent organic pollutants (POPs) risks to humans and wildlife. Hum Ecol Risk Assess 9:303–24

Sekizawa J and Tanabe S. 2005. A Comparison between integrated risk assessment and classical health/environmental assessment: Emerging beneficial properties. Proceedings of the 10th International Congress of Toxicology. Toxicol Appl Pharmacol 207, Issue 2, Suppl. 1:617–22

Sekizawa J, Suter GW II, and Birnbaum L. 2003. Integrated human and ecological risk assessment: a case study of tributyltin and triphenyltin compounds. Hum Ecol Risk Assess 9:325–42

Suter GW II, ed. 2003. Special Issue: Framework for integration of human and ecological risk assessment. Hum Ecol Risk Assess 9(1):267–386

Suter GW II, Vermeire T, Munns WR Jr, *et al.* 2003a. A framework for the integration of health and ecological risk assessment. Hum Ecol Risk Assess 9:281–301

Suter GW II, Munns WR Jr, and Sekizawa J. 2003b. Types of integration in risk assessment and management, and why they are needed. Human Ecol Risk Assess 9:273–79

Suter GW II, Vermeire T, Munns WR Jr, *et al.* 2005. An integrated framework for health and ecological risk assessment. Proceedings of the 10th International Congress of Toxicology. Toxicol Appl Pharmacol, 207, Issue 2, Suppl. 1:611–6

USEPA (US Environmental Protection Agency). 1998. Guidelines for Ecological Risk Assessment EPA/630/R-95/002F. Washington, D.C., USA

USEPA. 2003. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. 2000. Technical support document volume 2: Development of National Bioaccumulation Factors EPA-822-R-03-030. Office of Water, Washington, DC, USA

USEPA. 2004. Risk Assessment Principles and Practices. Staff paper. Office of the Science Advisor, Washington, DC, USA

Van der Jagt K, Munn S, Torslov J, *et al.* 2004. Alternative Approaches can Reduce the Use of Test Animals under REACH. Joint Research Centre, European Commission, Ispra, Italy

Vermeire T, MacPhail R, and Waters M. 2003. Integrated human and ecological risk assessment: a case study of organophosphorous pesticides in the environment. Hum Ecol Risk Assess 9:343–357

Waters MD, Selkirk JK, and Olden K. 2003. The impact of new technologies on human population studies. Mutation Res. 544:349–60

WHO (World Health Organization). 2001. Pesticide Residues in Food -2000 Evaluations. Part II—Toxicological Evaluation. WHO/PCS/01.3. Geneva, Switzerland

WHO/IPCS. 2001. Report on Integrated Risk Assessment.World Health Organization/ International Programme on Chemical Safety. WHO/IPCS/IRA/01/12. Geneva, Switzerland

Journal of Risk Research
Vol. 10, No. 6, 841–851, September 2007

Routledge
Taylor & Francis Group

ARTICLE

Evaluation of Human Health Risks From Exposures to Four Air Pollutants in the Indoor and the Outdoor Environments in Tokushima, and Communication of the Outcomes to the Local People

JUN SEKIZAWA*, HIROYUKI OHTAWA*, HIROSHI YAMAMOTO*, YASUSHI OKADA**, TAKESHI NAKANO**, HIROMICHI HIRAI†, SHOJI YAMAMOTO† & KEISUKE YASUNO‡

**Faculty of Integrated Arts and Sciences, Tokushima University, Tokushima, Japan, **Hyogo Prefectural Institute of Public Health and Environmental Sciences, Hyogo, Japan, †Tokushima Prefectural Institute of Public Health and Environmental Sciences, Tokushima, Japan, ‡Graduate School of Natural Sciences, Nagoya City University, Japan*

ABSTRACT The Law concerning Reporting etc., of Releases to the Environment of Specific Chemical Substances, and Promoting Improvement in Their Management (the so-called Pollutant Release and Transfer Register Law or the PRTR Law) was promulgated in Japan in 1999. Estimated amounts of the specific chemical substances released from their major emission sources to local environments are publicly available by law. Concentrations of benzene, toluene, xylene (i.e., volatile organic compounds or VOCs) and formaldehyde specified by law were measured in different seasons from 2003 to 2005 both at outdoor and indoor sites within the Tokushima University campus and in a nearby local area to estimate their human exposures. There were no substantial differences between the indoor and the outdoor concentrations of benzene, toluene, and xylene. Higher concentrations observed for formaldehyde in the indoor environment than in the outdoor environment in the 2003 winter season could be explained by the fact that there was renovation of the building nine months before the

Correspondence Address: Jun Sekizawa, Minami-josanjima, Faculty of Integrated Arts and Sciences, Tokushima University, Tokushima, Japan. Tel.: +8188-656-7263; Email: sekizawa@ias.tokushima-u.ac.jp

1366-9877 Print/1466-4461 Online/07/060841–11
DOI: 10.1080/13669870701342967

measurement. The exposure data obtained were used to evaluate the possible human health risks of these four chemicals by referring to their health criteria. The results indicated that the overall risks from the exposures to these chemicals both in the indoor and the outdoor environments were not significantly high even if fluctuations are taken into account. The results of our evaluation were released on the university website and also presented and discussed at a public meeting and three PRTR data seminars in the local society.

KEY WORDS: PRTR data, volatile organic compounds, formaldehyde, exposure assessment, health effects

Introduction

The Law concerning Reporting etc., of Releases to the Environment of Specific Chemical Substances, and Promoting Improvement in Their Management (the so-called Law for Pollutant Release and Transfer Register, or PRTR) was promulgated in Japan in 1999. The PRTR Law introduced a new concept to Japanese society in that protection of the environment and human health is promoted not through regulation but through disseminating of data on chemical releases from emission sources and with voluntary reduction of such chemical releases (Figure 1; Ohtawa *et al.*, 2004). However, several obstacles exist for people to understand the potential human health risks based on the data of the chemical release and transfer made available by the law. First, amounts of chemicals released in the environment from emission sources are not directly linked to possible human exposure concentrations, because chemicals go through processes including dilution, conversion and reaction after being released from emission sources, and no information on the total concentrations exposed to humans is available. Secondly, even if concentrations exposed to humans are available, toxicological information on each chemical must be integrated with exposure information to evaluate possible human health risks. Thirdly, people spend most of the time indoor, and thus, information of chemical concentrations in the indoor environment is important for estimating human

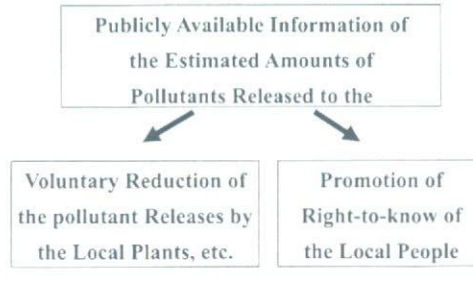

Figure 1. PRTR System is a New Paradigm for Environmental Protection in Japan

health risks from exposure to chemicals. We measured exposure concentrations of four chemicals in the local environment not only of outdoor, but also of indoor environment, and compared the results with health criteria to estimate human health risks. Our measurements were compared with the exposures estimated based on the local PRTR data using a model. Also, the significance of possible human health risks from the estimated exposures was evaluated using a health risk estimation model.

Methods

Chemicals, Sampling and Analysis

Indoor and outdoor concentrations of benzene, toluene, xylene (volatile organic compounds or VOCs) and formaldehyde were measured. The official methods described in the toxic air pollutant measuring method manual of the Air Pollution Control Division, Air Quality Bureau, Ministry of the Environment, Japan (1997) were used. Briefly, active sampling of the air was performed using Perkin Elmer ATD400 for thermal desorption sampler (SUPLECO) with pump, and high performance passive sampler, VOC TD (SUPLECO), was used in passive sampling each for 24 hour on certain days. Aldehyde was trapped by Sep-Pak XPoSure aldehyde sampler with Ozone Scrubber and DSD-DNPH passive sampler. VOCs were analyzed using gas chromatography/mass spectrometry (PerkinElmer ATD-400) equipped with thermal desorption apparatus at the Hyogo Prefectural Institute of Public Health and Environmental Sciences. Dinitrophenylhydrazone was analyzed using liquid chromatography (SHIMADZU LC-VP) equipped with Shim-Pack FC-ODS column.

Sampling Sites and Weather Conditions

Air samples were collected inside and outside of several chemistry laboratories (in the 2003 and 2004 period the outside samples were collected exclusively at our own laboratory) in the University of Tokushima, outside the Health Center in Komatsujima in a residential area where a sampling station is settled by Tokushima prefecture. A small amount of benzene was used several times in one laboratory, but other chemicals were not used in any laboratories before or during the sampling period. Weather conditions were mostly fine or cloudy on the sampling days.

Model Estimation of Exposure Data and Human Health Risk Estimation

AIST-ADMER, an atmospheric dispersion model for exposure assessment, and Risk Learning, a human health risk estimation tool developed by the Research Center for Chemical Risk Management (CRM) of the National Institute of Advanced Industrial Science and Technology, was used (AIST,

2005a, 2005b). Health criteria data such as RfC (reference concentration) or unit risk were cited from the IRIS database developed by the US Environmental Protection Agency (US EPA, 2005).

Meetings and Information Release on the Website

Meetings were held in a hall of the Tokushima University in 2004, and in the auditoriums in the local cities (Okayama, Osaka and Hyogo) to communicate our data and results of human health risk evaluation to the public. The latter were organized by either the New Energy and Industrial Technology Development Organization (NEDO) or the Kansai branch of the Japan Society on Water Environment in 2004 and 2005. The information was also released on the university website (Laboratory for Environmental Chemistry, 2005), although contents are currently given in Japanese.

Results

We selected four chemicals specified in the law, i.e., benzene, toluene, xylene, and formaldehyde, and measured their concentrations in the living environment in Tokushima in the period between autumn 2003 and spring 2005 to estimate their indoor and outdoor exposures. Toluene and xylene are reported to be the most abundantly released chemicals in the PRTR estimation nationwide and also in the Tokushima area (Table 1). Only PRTR data of the previous years are available for comparison, as data from each emission source are collected once per year and publicly available only after editing of the raw data, nationwide, is completed. Benzene is known to be a human carcinogen which is found in automobile exhausts, while formaldehyde is known to be an irritant to eyes and respiratory system which is released from adhesives used in wallpaper and other household goods.

Table 1. Estimated Amount of Chemicals Released in the Air of Tokushima Prefecture and Nationwide in the 2002 year period

	Release in the Air (ton/year)	
Chemical	Tokushima Prefecture	Nationwide
Benzene	6.3	1807
Formaldehyde	5.07	342
Toluene	92.8	122790
Xylene	56.9	47305

VOC Data

There were no substantial differences in the indoor concentrations of benzene, toluene, and xylene (VOCs), respectively measured at different occasions in the period from November 2003 through May 2005 as shown in Table 2a. Similarly, no substantial differences were seen in the concentrations of each VOC measured outside of our own laboratory or at the local air sampling station in this period (Table 2b). Although we applied passive sampling methods in the year of 2005, as compared to an active sampling method in the previous years, the measured concentrations were comparable and showed no difference due to the sampling methods. Furthermore, there were no statistically significant differences between the indoor concentrations (1.30 ± 0.64 for benzene, 6.04 ± 2.62 for toluene, 3.94 ± 1.56 for xylene; unit in $\mu g/m^3$) and the outdoor concentrations (1.30 ± 0.42 for benzene, 5.83 ± 3.37 for toluene, 3.18 ± 1.29 for xylene;

Table 2A. VOC Concentrations in the Indoor Environment ($\mu g/m^3$)

Benzene	2003 Winter *1	2004 Summer *2	2005 Spring *3	Summary
Range	0.89–2.0	1.4–1.7	0.41–2.54	0.41–2.54
Mean ± SD	1.40 ± 0.42	1.55 ± 0.21	1.25 ± 0.81	1.30 ± 0.64
Toluene	2003 Winter *1	2004 Summer *2	2005 Spring *3	Summary
Range	2.6–14.0	5.9–6.9	3.75–9.04	2.60–14.0
Mean ± SD	5.94 ± 4.00	6.40 ± 0.71	6.03 ± 1.74	6.04 ± 2.62
Xylene	2003 Winter *1	2004 Summer *2	2005 Spring *3	Summary
Range	3.4–6.3	3.3–3.6	1.56–6.68	1.56–6.68
Mean ± SD	4.70 ± 1.24	3.45 ± 0.21	3.51 ± 1.78	3.94 ± 1.56

Table 2B. VOC Concentrations in the Outdoor Environment ($\mu g/m^3$)

Benzene	2003 Winter *1	2004 Summer *2	Summary
Range	1.1–2.4	1.2–1.3	1.10–2.40
Mean ± SD	1.31 ± 0.48	1.25 ± 0.07	1.30 ± 0.42
Toluene	2003 Winter *1	2004 Summer *2	Summary
Range	2.2–13.0	6.3–8.1	2.20–13.0
Mean ± SD	5.44 ± 3.75	7.2 ± 1.27	5.83 ± 3.37
Xylene	2003 Winter *1	2004 Summer *2	Summary
Range	1.4–5.2	2.6–3.7	1.40–5.20
Mean ± SD	3.19 ± 1.46	3.15 ± 0.78	3.18 ± 1.29

*1 November 2003–January 2004 (n=7)
*2 June–July 2004 (n=2)
*3 April–May 2005 (n=10)

unit in $\mu g/m^3$) with respect to measured VOCs using t-test for the case showed no significant difference in variance.

Formaldehyde Data

High concentrations ($8.57 \pm 2.62\,\mu g/m^3$) were observed for formaldehyde in the indoor air sampled in the 2003 winter season, which decreased to $2.03 \pm 0.61\,\mu g/m^3$ in the 2004 summer season, and further in 2005 (Table 3a). A probable reason for the higher concentrations of formaldehydes in the indoor environment in the 2003 winter season could be that there was renovation of the building nine months before the measurement. A statistically significant difference ($p<0.01$, in the t-test) was seen for formaldehyde when the overall average of the indoor concentrations ($1.10 \pm 0.747\,\mu g/m^3$) of 2004 and 2005 period was compared against that of the outdoor concentrations ($1.93 \pm 0.535\,\mu g/m^3$) of the 2003 and 2004 period. A specific reason for the lower indoor concentrations as compared to the outdoor concentrations is not known, however the laboratory had been well ventilated after we started to keep experimental small fish in the 2004 summer period.

Comparison with Model Estimations by AIST-ADMER Using PRTR Data

In-air exposures of benzene, formaldehyde, toluene, and xylene in the Tokushima city area were cited from the NITE (2005) which estimated the average concentrations of pollutants in the area using AIST-ADMER with the PRTR data of 2002 period by using a 5 km mesh for the year-round emission and the pertinent meteorological data (Table 4). The estimated

Table 3A. Formaldehyde Concentrations in the Indoor Environment ($\mu g/m^3$)

	2004 Spring *1	2004 Summer *2	2005 Winter *3	Summary *4
Range	4.7–12.0 (n=6)	1.13–2.86 (n=11)	0.17–2.10 (n=22)	0.17–2.86 (n=33)
Mean ± SD	8.57 ± 2.62	2.03 ± 0.61	0.67 ± 0.374	1.10 ± 0.747

Table 3B. Formaldehyde Concentrations in the Outdoor Environment ($\mu g/m^3$)

	2004 Spring *1	2004 Summer *2	Summary
Range	1.3–2.7 (n=10)	0.60–2.98 (n=14)	0.60–2.98 (n=24)
Mean ± SD	1.89 ± 0.407	1.96 ± 0.625	1.93 ± 0.535

*1 November 2003–January 2004
*2 June–September 2004
*3 February–May 2005
*4 Summary : April 2004–May 2005

Table 4. Exposure Estimation by AIST-ADMER using Local PRDR Data in the 2002 period ($\mu g/m^3$)

Chemical	Estimated Exposure Data	Measured Outdoor Concentrations
Benzene	0.193	1.30
Formaldehyde	0.226	1.93
Toluene	3.35	5.83
Xylene	1.72	3.18

exposure concentrations of toluene and xylene were fairly close to our measured data, however estimated values for benzene and formaldehyde were lower than our measured data. Since our measurements were limited in the location and in frequency, they may not represent the general conditions of air pollution in Tokushima area and/or the emission sources for formaldehyde and benzene may have been localized in the area where our sampling was made.

Human Health Risk Estimation

Significance of the possible health risks were evaluated for human exposures of benzene, formaldehyde, toluene and xylene for indoor, outdoor and time-weighted combination of the two environments assuming that humans spend 21 hours in the indoor environment and 3 hours in the outdoor environment on average (Griffin, 1994), and against the health criteria shown in Tables 5a and 5b. Concentrations of all chemicals were lower than either the air quality standard or the indoor air quality guideline values. Provisional estimation of possible human health risks was performed using Risk Learning based on a

Table 5A. Health Criteria for Pollutants

Chemicals	Toxicity	Health Criteria	
		$\mu g/m^3$	(ppm)*3
Benzene	Leukemia (Annual average value)	3 *1	_
Formaldehyde	Irritation to Eyes and Respiratory Tract	100 *2	(0.08)
Toluene	Neurotoxicity Developmental Toxicity	260 *2	(0.07)
Xylene	Neurotoxicity Developmental Toxicity	870 *2	(0.20)

*1 Air Quality Standard, Ministry of the Environment, Japan
*2 Indoor Air Concentration Guideline, Ministry of Health, Labor and Welfare, Japan
*3 Converted values from $\mu g/m^3$

Table 5B. Risk Estimation for VOCs and Aldehydes

Chemicals	Ratio*		
	Indoor	Outdoor	Combined
Benzene	0.43	0.43	0.42
Formaldehyde	0.0056	0.02	0.0071
Toluene	0.023	0.022	0.022
Xylene	0.0045	0.0037	0.0042

* Ratio of the Environmental Concentrations to the Standard or Guideline Values

scenario that humans spend 21 hours in the indoor environment and 3 hours in the outdoor environment on average and shown in Table 6.

The excess cancer risks from exposures to benzene and formaldehyde are in the orders between 10^{-5} and 10^{-6}. Hazard quotients were less than 0.1 for the measured concentrations of these chemicals when compared to the health guidance values estimated by the U.S. Environmental Protection Agency.

Risk Communication

We communicated the results of our exposure measurements and evaluation of possible human health risks associated with the measured concentrations of benzene, formaldehyde, toluene and xylene on several occasions at public

Table 6. Human Health Risk Estimation Using Risk Learning

	Exposure	Average exposure ($\mu g/m^3$)	Unit Risk or RfC*1	Cancer Risk *2 or HQ *3	Summed Risk for Indoor and Outdoor Exposure
Benzene	Indoor	1.1E+00	7.8E−06	8.52E−6 3.6E−2	9.74E−6 *2
	Outdoor	1.6E−01	30 *1	1.22E−6 5.2E−3	4.12E−2 *3
Formaldehyde	Indoor	9.6E−01	1.3E−5	1.25E−6	4.39E−6 *2
	Outdoor	2.4E−01		3.14E−6	
Toluene	Indoor	5.1E+00	4E2 *1	1.27E−2	1.44E−2 *3
	Outdoor	7.0E−01		1.75E−3	
Xylene	Indoor	3.3E+00	1.00E2 *1	3.3E−2	3.68E−2 *3
	Outdoor	3.8E−01		3.81E−3	

*1 RfC: Reference Concentration estimated by the US EPA
*2 Cancer Risk = Unit Risk × Average Exposure
*3 HQ: Hazard Quotient = Average exposure/RfC

meetings such as one in our campus, and three others in the local PRTR data seminars, as well as through the release of the information on our university website in an attempt to educate the university students and the local people, to stimulate discussions among them, and to increase their awareness and understanding on the relationship between their health and the environment. Although the detailed analyses of the feedback of the audiences in the meetings or of the people accessing the information on the website are not ready, our preliminary assessment indicates that they showed increased awareness about environmental pollutions and interests in learning more about the quality of the environment in Tokushima.

Discussion

Humans are exposed to various toxic chemicals from different sources. The estimated amounts of toxic chemicals released from major emission sources to the local environments are publicly available by the PRTR law. Since many people now spend most of their time in the indoor environment, comparisons were made between the indoor and the outdoor air concentrations of four toxic chemicals, and the measured data were further compared with several health criteria to assess the quality of the current living environment in Tokushima. Due to the limitations in the sampling frequency and the number of sampling sites, it is not possible to draw a solid conclusion in this study. However, our study provided an example of comparisons of the indoor and the outdoor exposures of four widely used chemicals in the environment, as well as making use of newly available PRTR data on environmental release of these chemicals from emission sources to understand potential human health effects of their exposures in the local environment in Tokushima.

Provisional Risk Evaluation for VOCs

Although the margins between the air quality standard and measured concentrations were narrow for benzene, considering the fact that the air quality standard for benzene was established based on the excess cancer risk of $3–7 \times 10^{-6}$, the estimated level of current risk is not considered seriously high. Recently, CRM published a risk assessment document on toluene in which they described that AIST-ADMER estimation of environmental exposure can be lower for the area of less population as compared to the dense population area (CRM, 2005). CRM suggests that indoor air concentration may vary among houses and also from day to day. We collected the air samples of both the indoor and the outdoor environments of our laboratory on the same day to eliminate the possible day-to-day fluctuations but there may have been other factors affecting the comparison of the indoor and the outdoor concentrations. In their toluene human health risk assessment, CRM assessed the distribution of population in terms of

possible effects of toluene exposure to decrease the quality of life, which makes it difficult to directly compare our assessment with theirs.

Provisional Risk Evaluation for Formaldehydes

Since there was a wide margin between the measured concentrations of formaldehyde and the air quality guideline value, the current levels may not pose a significant human health risk. IPCS (2002) published a *Concise International Chemical Assessment Document on Formaldehyde* in which they cited the indoor and the outdoor air concentrations of formaldehyde in Canada. The median of the outdoor concentrations was 2.8 $\mu g/m^3$ and that of the residential indoor concentrations was 28.7 $\mu g/m^3$ or 29.7 $\mu g/m^3$ (IPCS, 2002). Although IPCS used the data from a large scale survey in Canada, the indoor concentrations were higher when compared to our data. The difference may be attributable to the possible high use of formaldehyde in the furniture and other household goods in Canada.

Conclusion

(1) Except with formaldehyde, no substantial difference was seen between the indoor and the outdoor concentrations of the chemicals measured in our study. From these data, we can estimate daily exposure levels both from indoor environment and from outdoor environment. It also prompts us to identify the possible sources of pollution to reduce exposures.

(2) We selected four chemicals which may potentially affect our health through environmental exposure. Toluene and xylene are most abundantly released from emission sources to the environment. Benzene is a known human carcinogen and detected in not negligible amounts in the environment. Formaldehyde is known to be an irritant to eyes and the respiratory system. Our data indicated that the current exposure levels of these four chemicals in the living environment in Tokushima are not likely to cause adverse effects to human health.

(3) The outcome of our study was communicated to our university students and the local people at several meetings and through the university website in an attempt to increase their awareness on the relationship between their health and the environment conditions. The level of consciousness on the health in relation to environmental pollutant exposure in daily life is still not very high. It is necessary to translate the available data in such a way that people can easily understand the relationship between chemical exposures and possible health effects. To enhance the knowledge of chemicals used in our daily life and their possible health effects among the public, we encourage further communication.

References

AIST (2005a) ADMER version 5.1. Available at http://www.riskcenter.jp/ADMER/ja/index_ja.html (accessed 10 April 2007).

AIST (2005b) Risk learning. Available at http://www.riskcenter.jp/RL/download.html (accessed 10 April 2007).

CRM (2005) Risk assessment document for toluene, research center for chemical risk management (Tsukuba, Japan: the National Institute of Advanced Industrial Science and Technology).

Griffin, R. D. (1994) *Principles of Air Quality Management* (Chelsea, London: Lewis Publications).

IPCS (2002) *Concise International Chemical Assessment Document No. 40, Formaldehyde* (Geneva: World Health Organization).

Laboratory for Environmental Chemistry (2005) Colaborative work with local institute on human exposure to indoor air pollutants. Available at http://www.ias.tokushima-u.ac.jp/envchem/welcome-english.htm (accessed 10 April 2007).

NITE (2005) National institute of technology and evaluation. Available at http://www.prtr.nite.go.jp/prtr/densitymap.html (accessed 10 April 2007).

Ohtawa, H., Sekizawa, J., Okada, Y., Hirai, H. and Yasuno, K. (2004) Human exposure to air pollutants in the indoor and outdoor environment. Paper presented at the International Joint Conference on Risk Assessment and Management, Seoul, November.

US EPA (2005) IRIS database for risk assessment. Available at http://www.epa.gov/iris (accessed 10 April 2007).

日本リスク研究学会誌 17(1)：79－84(2007)

【シンポジウム】

シンポジウム講演 5

内分泌かく乱化学物質による低用量影響の蓋然性

Biological Plausibility of Low-Dose Effects of Endocrine Disruptors

関澤　純*

Jun SEKIZAWA

先ほど学会総会でごあいさつをさせていただきました徳島大学総合科学部の関澤でございます。私は日本リスク研究学会のほかに日本トキシコロジー学会にも入っており，安全性評価あるいはリスク評価に関心を持って研究していますので，そういう観点からお話しを進めることにします。

このシンポジウムの企画について今日のオーガナイザーの間正さんからご相談を受けたことがありました。本日，私の前に遠山先生がおっしゃったように，ダイオキシンや環境ホルモン問題についてある程度沈静化し，あるいは巻き返しとして騒ぎすぎだったのではないかというご意見もあります。しかし最近になっていろいろ新しいことが見つかりつつあって，私はより深く検討する必要があるだろうということをお話しさせていただきたいと思います。

さてIPCSについてはご存じでない方もおられると思いますが，International Programme on Chemical Safetyの略で，日本語では国際化学物質安全性計画と呼ばれる国連の組織の一つです。私は徳島大学に移る前は国立医薬品食品衛生研究所で，化学物質のリスク評価を担当してこのIPCS関連の仕事を主にやってきました。IPCSは化学物質のリスク評価では国際的に信頼性の高い組織ですが，2002年にGlobal Assessment of the State-of-the-Science of Endocrine Disruptorsという内分泌かく乱化学物質についての国際的な専門家グループによる報告書をまとめました（IPCS, 2002）。そこに書かれている幾つかの大事なことをご紹介します。まず一つは内分泌かく乱化学物質と内分泌系をかく乱する可能性のある物質，英語ではEndocrine DisruptorsとEndocrine Disrupting potentialを持つ Hormonally Active Substancesとを概念的に区別すべきであるということです。すなわち内分泌かく乱とは生体レベルの事象であって，試験管内の現象とは概念的に区別すべきであるということです。先ほどの井口先生のお話しでもありましたが世界的にホルモン活性を持つ物質はさまざま見つかっていて，2000くらいあるというお話しもありました。しかしその中で本当に内分泌をかく乱する可能性のある物質というものは，おそらく非常に限られるだろうと思われます。次に内分泌かく乱化学物質については，当初考えられたようなエストロゲンすなわち女性ホルモン活性を持った物質か，アンチアンドロジェン，すなわち抗男性ホルモン活性を持った物質，また甲状腺ホルモンレセプターに反応する物質に限らず，さまざまな物質があり得るということは井口先生のお話しの中でも紹介されました。

さて今日私のメインテーマは，低用量影響リスクの評価ということです。これについて私は厚生労働科学研究の研究班に入れていただき，現在もその研究を続けております。今日はその研究成果の一端を紹介したいと思います。

本学会の皆さんはよくご存じかと思いますが，化学物質のリスク評価では，有害性の確認，用量―反応評価，暴露評価，リスク判定というステップをとるということが国際的に合意されています。そのうちの用量―反応評価についてですが，図1に示ししましたように，ある毒性については用量を増やしていくと毒性が増強されるというのが一般的で，ある濃度以下では毒性が見られなくなるという種類の物質と，いくら濃度を下げても非常に微少だけれども毒性が見つけられる，いわゆる

* 徳島大学総合科学部（Faculty of Integrated Arts and Sciences, University of Tokushima）

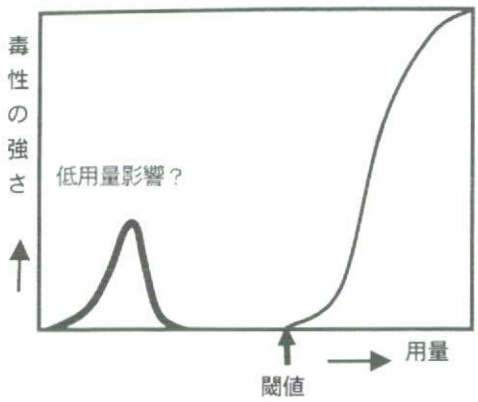

図1　通常の毒性試験における閾値以下の濃度（低用量）での反応の可能性を示す模式図

遺伝子に傷を付けるような発がん性物質の2種類に大別されています。

前者の場合に，動物実験などで毒性が見られなくなる濃度を閾値と呼んでおり，この閾値を安全係数あるいは不確実係数により割って，人における許容基準あるいは一日許容摂取量を求めています。この手法が種々の化学物質の安全性評価の基本として，食品添加物，食品汚染物，残留農薬などについて守るべき基準とされるわけです。ところが内分泌かく乱化学物質で指摘された大きな問題の一つは，図1のように閾値と言われる濃度，つまり濃度を下げていくと何の影響も見られなくなる濃度よりもさらに低い濃度で，何かの反応が見られることがあるということです。ホルモン活性を持つ物質についていえば，実はこのことは不思議でも何でもないことですが，必ずしもそのことが十分理解されていなかったことがあったほかに，この低用量での影響がもし有害ないし不可逆的なものである時にどう考えるかということが問題となりました。この問題については2000年に米国環境保護庁と，米国毒性プログラム(NTP)が共同して低用量影響評価ワークショップを開き検討しました（NTP，2001）。

ここで低用量作用とはヒトの通常の暴露の範囲あるいはアメリカ環境保護庁が，生殖・発生毒性評価のために決めた標準試験法で，一般に使用される用量よりも低い用量で起きる生物学的変化と規定しました。このワークショップの結論としては，幾つかの試験データはこの低用量影響を示唆しているが，必ずしも再現性が見られていないので，さらに深い検討が必要であるというところにとどまりました。しかしご存じのように，体内に既に天然のホルモン活性を持ったエストロゲンなどがあって，それらが時期や生体の必要に応じて増減することで体の機能を調節しています。その調節が適切に保たれ，ある範囲でバランスを取るということが非常に大事になっています。わかりやすい例が女性の生理を支えている女性ホルモン物質です。ところがこのホルモン活性物質については，生体内でシグナルクロストークという物質間の相互作用があります。先ほど紹介がありましたように，アリルハイドロカーボン受容体（ダイオキシン受容体とも通称される）と，エストロゲン受容体が相互作用することが知られています。そういった受容体間の相互作用には本来的な意味があるだろうということ，それから生体内のホルモン物質濃度の多少によるフィールドバックによる生体の恒常性（ホメオスタシスと言う）があるため，これまで考えられていた毒性評価とは違うような問題が，検討されなければいけないということです。私はこういう背景から，内分泌かく乱化学物質の問題というのは，毒性学的に新しい種類の問題であり，毒性評価の上からも生物学の基本に関係した幾つかの問題を深く検討しなければいけないと考えます。

また環境中の生物で見られた現象については，先ほどのご紹介ではメダカで陽性反応が見られたが，ヒトでは陰性の反応結果だったというお話しもありました。野生生物への影響と，ヒトの健康への影響の関係を生物学的メカニズムや，両者における暴露経路とか曝露量，そういったことを考えながら検討する必要があると考えます。次世代への影響の可能性や，リスクにおける不確実性の検討など深く考えておくべき課題が提供されたと思います。

少し長くなるので時間を節約しますが，具体的には特定の暴露時期，クリティカルウインドーあるいは臨界期と呼びますが，この時期の曝露による特別の影響，特に発生の非常に限られた時期におけるある種の薬物への暴露により，特定の臓器が影響を受ける可能性，また暴露を受けた結果が後の特定の時期に初めて検出される可能性があります。

食品中の残留農薬についての安全性試験とか，食品添加物などに課せられている試験には，多世代の繁殖試験がありますが，その場合は交配，妊娠，出産，授乳，その後の時期にわたり，継続的