Opening Address I

Greetings

Endocrine disrupters (EDs) have become the focus of great concern among the general public over their adverse effects on human beings and wildlife, however there is still much to be scientifically explored, which has made EDs a key environmental safety issue.

Therefore, the Ministry of the Environment, Japan (MOE) has been conducting environmental monitoring and hazard assessment, and also has been engaged in the exchange of information with other countries and international organizations under a framework of international coordination.

As a part of these activities, the MOE has started developing testing methods using Medaka, one of the ideal models for the research and testing for toxicology so as to evaluate the effects of endocrine disrupters.

This symposium is planned to discuss the development of testing methods of endocrine disrupters using Medaka, building networks among researchers.

I earnestly hope that it will be a valuable conference that could contribute to new advances in this field.

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Opening Address II

Activities of Fish Drafting Group under the MOE Program with Endocrine Disruptors

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It is an honor and my pleasure to open the Third International Medaka Symposium at the Okazaki Conference Center. The previous two symposia occurred in Nagoya.

Research and policy activities concerning endocrine disrupter in the Ministry of the Environment (MOE) were initiated in 1998 with the release of the document entitled “Strategic Programs on Environmental Endocrine Disrupters (SPEED’98)”. Following this initial program, a major research project was launched in 1998 .The purpose of the project was to develop screening tests and evaluate the endocrine disruptive effects of 65 substances. Since its initiation in 1998, the MOE project has progressed with research activities focused on mammals and other species important to ecosystem health, including fish, birds and amphibians.

One of these activities initiated by the MOE involves the development of testing methods using medaka. As part of this MOE sponsored research project, the Fish Working Group for Development of Screening Tests and Testing was established in 1999. The aim of the Fish Working Group is to develop testing methods using medaka that can eventually be submitted as draft protocols to the OECD.

At the time this group was established, it was very important to determine what biological effects various endocrine disruptors induced and whether those responses changed based on the sensitivity at any given stage during the fish life cycle. Further, it was important to determine what kinds of chemicals had biological effects and whether the changes induced were similar to those observed in other species. Fish full life cycle tests have been started to confirm the effects of a number of reference chemicals, such as estradiol-17â, ethynylestradiol and methyltestosterone, using **medaka**. For the second stage of these studies, partial fish life stage toxicity testing and reproduction testing has been developed. Further, new **medaka** strains, such as FLF and d-rR have been used for the development of these tests. *In vitro* studies also have been developed in order to screen many of the

chemicals of concern.

Today, we have the pleasure of listening to a special lecture in the area of fish sexual differentiation. In this presentation, the sex-determination gene of medaka, DMY (Y-specific DM-domain gene) will be discussed. This gene is the first to be found in non-mammalian vertebrates.

In conclusion, I am very pleased to open this meeting where I believe there will be a great opportunity to share useful information and I am confident that this meeting will be useful and successful for all.
Thank you for your attention.

Opening Address III

Status of the OECD Special Activity on Endocrine Disrupters Testing and Assessment

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The OECD endocrine disrupter activity was initiated in November 1996 at the request of OECD Member countries and industry. A Task Force on Endocrine Disrupter Testing and Assessment (EDTA) was then established to manage the OECD activity on endocrine disrupters in late 1997. The objectives of the EDTA Task Force are to:

- Identify the needs and prioritize the development of new and enhanced guidelines for the detection and characterization of endocrine disrupting chemicals;
- Develop a harmonized testing strategy for the screening and testing of endocrine disrupters;
- Manage validation work for newly developed and enhanced Test Guidelines as appropriate; and
- Provide practical tools for sharing of testing results and assessments.

A major achievement of the EDTA Task Force has been the definition of an initial framework capturing the potential screening and testing needs in both human health and ecotoxicological areas. The framework attempts to identify tests at different of levels of biological and regulatory complexity: from their interactions with hormone receptors to tests in whole animals at different sensitive life stages and tests where effects might be passed to the next generation.

The EDTA Task Force validation work on new and enhanced methods aims to ensure the reliability and relevance of testing methods in order to allow regulatory acceptance. This validation work is in accordance with the OECD Solna principles, recognized by many centers involved in the validation of test methods (ECVAM, ICCVAM).

The Validation Management Groups (VMG) have been established to co-ordinate and oversee the conduct of method development and validation in three

basic areas: i) mammalian toxicological tests, ii) ecotoxicological tests, and, in the near future, iii) *in vitro* and other non-animal tests.

The VMG for mammalian tests selected three *in vivo* tests as priorities for further development and international validation: the rodent uterotrophic assay (estrogen and antiestrogen activities), the rodent Hershberger assay (androgen and antiandrogen activities), an enhanced Guideline 407 (Repeated dose toxicity) to evaluate several new endocrine related parameters. Validation work is completed for the rodent uterotrophic assay and an independent peer-review will be organized. Validation work is well underway for the Hershberger assay and the enhanced TG 407.

The VMG for ecotoxicity tests oversees the development and validation of test methods for fish, birds and amphibians and it will soon start discussion on invertebrates testing. The work is at an early stage of development. Pre-validation studies for a fish screening assay will start in 2003, endpoints covering (anti) estrogen, aromatase inhibitors and (anti) androgen activities are included. Methods involving fish sensitive life-stages and full life cycle will be considered in higher tiers. Activities on an amphibian metamorphosis assay were proposed by Members countries to address chemicals disrupting the thyroid function. Two avian reproduction tests are being considered: a 1-generation study and 2-generation study.