Current Strategies against Environmental Endocrine Disrupters by the Ministry of the Environment, Government of Japan

Hironori Hamanaka
Ministry of the Environment, Government of Japan

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My name is Hironori Hamanaka and I am the Vice-Minister for Global Environmental Affairs for the Ministry of the Environment, Government of Japan.

On behalf of the Ministry of the Environment, I would like to thank you all for participating in the symposium. Today I would like to talk about what the Ministry of the Environment is doing about the problem of environmental endocrine disrupters.

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In 1996, the American scientist, Dr. Theo Colborn revealed the existence of environmental endocrine disrupters, which have been known as "environmental hormones" in Japan, in her book under the title "Our Stolen Future." We in Japan as well as other countries of the world became more concerned about environmental endocrine disrupters when their existence was revealed.

The liaison council for government agencies was established in 1997 to coordinate efforts of all agencies. The then Environment Agency announced the "Strategic Programs on Environmental Endocrine Disrupters '98 (SPEED '98)" and prepared a list of 67 substances suspected of having an endocrine disrupting effect.

The same year, the Environment Division of the Liberal Democratic Party (LDP) established the Subcommittee of Endocrine Disrupters. The Millennium Project was started in 2000 under the leadership of the late Prime Minister Keizo Obuchi. One of the programs of the Millennium Project was to have assessed toxicity of over forty substances over a period of three years.

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The Ministry of the Environment has proceeded to address the problem of environmental endocrine disrupters (EDs) in accordance with SPEED '98.

The mainstays of the Ministry of the Environment efforts are as follows:

(1) Promotion of environmental fact-finding studies

(2) Promotion of testing, research and technology development

(3) Assessment and management of environmental risk, provision of related information

(4) Efforts for establishment and reinforcement of international networking on endocrine disrupter issues

Initiatives of the Ministry of the Environment are based on these four mainstays.

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Now I would like to talk about the Ministry of the Environment's system for dealing with EDs. The first step is to get a grasp on the actual condition of the environment. At the same time, we develop the test method and assess toxicity of the substances using the test method developed.

We then assess risk together with the results of both and then conduct risk management based on those results.

When taking these measures, it is also necessary to work together with the international community. We therefore hold international symposiums and conduct international cooperative research.

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Now I would to give a brief description of the results of the environmental monitoring survey of endocrine disrupters conducted in 2001.

The study primarily involved 65 substances listed on SPEED ’98 in water, sediment, air, and in the bodies of wild animals. Of a total of 64 substances, 45 were detected. Details are available on the Ministry of the Environment’s Web site.

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Next I would like to talk about the exact procedure of risk assessment for the substances listed on SPEED ’98.

First we research literature available on the listed substances. After having the reliability of the literature assessed by experts, the results of the environmental monitoring survey are taken into consideration and we study whether it is required to conduct screening/testing for each of the substances, and if it is required, we study the method.

Concerning the existence and degree of endocrine disrupting effect, we comprehensively consider the results of the literature study and environmental monitoring survey as well as screening/testing results. We then assess risk along with general toxicity.

Next we assess risk taking exposure assessment into consideration, and then conduct risk management in accordance with the results.

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I would now like to talk about the specific screening/testing method for mammals. Along with conducting the improved one-generation test that takes endpoints and concentration of each substance into account, we are conducting *in vitro* tests called a receptor binding assay and reporter gene assay to check bonding affinity with receptors to compensate for the results of those *in vivo* tests.

We are also conducting the uterotrophic assay, the Hershberger assay and revised 28-day repeated-dose toxity administration test, in collaboration with the concerned agencies, which the OECD is verifying. We are furthermore compiling results that take those into consideration.

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As for the test results, with the exception of nonylphenol and 4-octylphenol, we have completed testing for 10 of 12 of the priority substances selected for testing in 2000.

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As for evaluation of toxicity of the 10 substances, no clear endocrine disrupting effect was observed for low dosages considered to be the estimated human exposure level for any of the substances.

At the present point in time, however, the connection with endocrine disruption is unknown for some of these substances, but a significant variation in representation of messenger RNA (mRNA) and concentration of hormones in the blood was observed. The significance of this should become apparent as more data is collected in the future.

These results were reported at the OECD conference held in Tokyo in June last year and are provided on the OECD Web site.

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I would now like to talk about the specific screening/testing method for fish. In Japan *medaka* are used as the test fish. Along with using the partial life cycle test for exposure and observation from egg to maturity and the full life cycle test that covers from egg to maturity and on to the next generation, we also conduct *in vitro* tests called the receptor binding assay and reporter gene assay to check bonding affinity with receptors to compensate for these test results.

The OECD is now verifying results of the vitellogenin production test that uses a protein called vitellogenin which is a precursor to vitelline protein ordinarily produced in females as an index for feminization and we are also conducting those tests ourselves.

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This slide shows the *medaka* test facilities at the Environmental Endocrine Disrupter Laboratory established in March last year at the National Institute for Environmental Studies. The Environmental Endocrine Disrupter Laboratory is the hub for investigative research on endocrine disrupters. In addition to toxicity tests using *medaka*, an endocrine disrupter database is also being constructed.

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The testing of all 12 priority substances selected in 2000 that are shown in the slide using fish has now been completed.

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Here are the results of toxicity assessment of these substances. Nonylphenol and 4-octylphenol used as raw materials for industrial detergents have a strong affinity to bind with female hormone receptors of fish. Expression of testis-ova has been observed in the testes of fish and the substances have been observed to have an endocrine disrupting effect.

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This slide shows gonad tissue of *medaka* administered nonylphenol. A shows normal testes and B normal ovaries. In C and D we can find oocytes that become ova in testes.

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Here is a summary of test results for nonylphenol and 4-octyl phenol. First of all, in the receptor binding assay that measures affinity of the chemicals to bind with estrogen receptors, nonylphenol has approximately 1/10 the affinity of female hormones and 4-octylphenol approximately 1/15.

In the vitellogenin production assay, partial life cycle test and full life cycle test, the affect was observed at the concentration shown in the table. If we make the concentration where testis-ova were expressed the Low Observed Effect Concentration (LOEC) and the next lower concentration the No Observed Effect Concentration (NOEC), the NOEC for nonylphenol is 6.08 μg/l and 9.92 μg/l for 4-octylphenol.

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As was explained by the slide we saw a little while ago, the NOEC is established based on concentration where testis-ova are expressed. If we multiply the NOEC by the safety coefficient of 1/10 to get the estimated NOEC, we get 0.608 μg/l for nonylphenol and 0.992 μg/l for 4-octylphenol.

This table shows a comparison of these values with the results of an environmental monitoring study conducted by the Ministry of the Environment.

Although concentration of 4-octylphenol in water is way below the estimated NOEC, concentration of nonylphenol in some places exceeds estimated NOEC.

Based on these results, the Ministry of the Environment feels that the level of nonylphenol in the aquatic environment of Japan is enough to have an effect on fish, and has provided agencies in charge of these industries with information and has instructed them to advise companies to take voluntary measures such as switching to substitutes for these chemicals.

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This is a continuation of the results of the toxicity assessment (fish). No clear endocrine disrupting effect has been observed for chemicals other that nonylphenol and 4-octylphenol.

Testis-ova have been observed to be expressed in the testes at a low rate of occurrence for some substances such as ester phthalates and benzophenone. Additional testing is now being conducted, and the substances will be evaluated based on the results.

Just as with mammals, the results of these additional tests have been published on the Ministry of the Environment's Web site. The results were reported at the OECD conference held in Tokyo at the end of June this year and are also available at the OECD's Web site.

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Here is a list of substances for which we have begun to evaluate risk in 2000 and 2001. Just as I mentioned a little while ago, we have already gotten the toxicity assessment results for most of the substances chosen in 2000.

We are currently evaluating toxicity for the substances selected in 2001, and we plan to compile the results from spring through summer next year.

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Here is a list of substances for which we have begun to evaluate risk in 2002. These substances were selected at the meeting of the Association for Research of the Endocrine Disrupter Problem held in October this year.

Of the group of 65 substances listed on SPEED ’98, 24 substances were selected excluding 20 pesticides registered by the Pesticide Control Law, such substances as dioxins and PCBs being studied by other departments of the Ministry of the Environment, and other substances selected for risk evaluation in 2000 and 2001.

Of these, animal experiments are being conducted for the 8 substances shown in yellow (from the standpoint of pros and cons concerning estimated exposure of human beings or fish and establishment of dosage for animal test using fish or human beings). A literature search is still being conducted for the remaining 16 substances shown in white.

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These are the measures being taken by the Ministry of the Environment. There is however still much we do not know about endocrine disrupting chemicals. To address this problem, it will require international cooperation and contribution to the OECD initiatives. We also feel it is important to conduct cooperative research such as the joint research between Japan and the UK and Japan and Korea, and to hold international symposiums such as this.

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Future themes include:

(1) Conducting environmental fact-finding studies and risk evaluation

(2) Promotion of technical development

(3) Promotion of international initiatives

(4) Promotion of risk communication

(5) Review of SPEED ’98

(4) and (5) in particular are new initiatives. The Ministry of the Environment will continue to actively tackle the problem of endocrine disrupters. We ask you continued understanding and cooperation.

Thank you for your attention.