

MOE' s Perspectives on Endocrine Disrupting Effects of Substances

ExTEND 2005

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Ministry of the Environment, Japan (MOE)

The EXTEND 2005 subtitle is an acronym for Enhanced Tack on Endocrine Disruption, followed by the year the document was created.

Introduction

The Ministry of the Environment, Japan (MOE) devised the “Strategic Programs on Environmental Endocrine Disruptors” in May 1998, made revisions and additions based on more recent knowledge in November 2000, and issued a November 2000 version (hereafter called SPEED '98). In accordance with this program, research on the mechanisms of endocrine disruption has progressed, along with environmental monitoring, test development and implementation through the Millennium Project, as well as annual international symposia and collaborative research between Japan and the United Kingdom of Great Britain and Northern Ireland(UK), or between Japan and the Republic of Korea.

International activities in which MOE has participated include the completion of the “Global Assessment of the State of the Science of Endocrine Disruptors” in August 2002 (hereafter “WHO Global Assessment”, also available in Japanese translation), by the World Health Organization (WHO), International Labor Organization (ILO) and the United Nations Environmental Program (UNEP). During this time, at the Organization for Economic Cooperation and Development (OECD), MOE has made specific proposals and is proceeding with trials on test method development for endocrine disruptors, and new knowledge has continued to accumulate through a variety of efforts.

In May 2003, the government’s definition of endocrine disruptors was agreed as follows “Injury and/or Hazardous Effects on Organisms Caused by Exogenous Substances Through Influence on the Endocrine System”.

MOE established a SPEED '98 Revision Working Group in 2003, composed of specialists, experts in the field, and representatives from consumer groups etc. (hereafter called “Revision WG”). This Revision WG held meetings for two years and created a brochure on the achievements of the activities under SPEED '98 for the general public. It also compared the activities and results of SPEED '98 thus far to the issues that have been indicated internationally, and identified issues for the future. The Revision WG also held hearings from local governments on this problem.

Through this process, MOE has developed this document “ MOE’s Perspectives on Endocrine Disrupting Effects of Substances-ExTEND 2005-” (hereafter called “ExTEND 2005”)

In addition to continuing to diligently conduct the necessary survey and research on endocrine disruptors as part of the continuing comprehensive measures to deal with chemicals based on ExTEND 2005, MOE will continue to make every effort to promote the information sharing and communication for the better understanding of general public.

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Environmental Health and Safety Division,
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Ministry of the Environment

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I. Activities to Date

1. Basic Framework of SPEED '98

With regard to the problem of endocrine disruptors, MOE stated in 1998 that “Environmental contamination by exogenous endocrine disruptors (so called environmental hormones) may be linked to the impairment of reproductive functions and the occurrence of malignant tumors through the disruption of the endocrine systems in humans and wildlife. At the present time, there are many questions still left unanswered by science, although these issues are related to the basic conditions for survival of living creatures, and may even have serious consequences for future generations, making this an important issue for environmental preservation.”

The framework of SPEED '98 included (1) progress on detection in the environment and surveys of the wildlife, (2) promotion of test research and technology development, (3) proceeding with environmental risk assessments, environmental risk management and provision of information, (4) efforts to strengthen the international network. For the specific action planning, 67 chemicals were identified as chemicals having the highest priority in the survey and research in order to clarify the presence, the strength and the mechanisms of endocrine disrupting effects of each chemical. Subsequently, this list was revised to 65 chemicals in November 2000, and the various efforts have progressed.

2. Specific Measures of SPEED '98

(1) Environmental Surveys for Chemicals and Surveys of Effects on Wildlife

Since 1998, measurements of the concentrations of the chemicals listed in SPEED '98 have been conducted for wildlife and four media, water, sediment, soil and air (Table 1).

There has also been development of survey methods and partial surveys of the concentrations in indoor atmospheres, aquatic organisms, wild animals, as well as in food samples.

The results of the environmental surveys have been used as the basic data to select the chemicals for which tests will be implemented in order to assess the hazard and also to establish test concentrations (doses). In addition, the environmental concentration data itself can also be used effectively for general countermeasures to chemicals.

In the surveys of the effects on wildlife, it was shown that the females of the rock shell (*Thais clavigera*) had abnormal sexual organ development, with the formation of male type sex organs, over a wide range of the Japanese coastline. This was the evidence to be caused by organotin compounds, tributyltin and triphenyltin from antifouling paints in the marine environment.

On the other hand, surveys were conducted based on existing reports of elevated concentrations of vitellogenin, which is a protein that is a component of egg yolks, in male koi, but there was no causal relationship found between the detection of specific substances in the body of koi and abnormalities. There were also surveys conducted on frogs, covering the regions where the appearance of frogs with extra legs etc. are known to be obvious, but there was no causal relationship found between the detection of specific substances in the body and abnormalities.

Table 1 Implementation of Environmental Surveys and Impact Surveys for SPEED '98

	Environmental survey				Indoor air survey	Aquatic organisms ¹ (fish, shellfish)	Wildlife survey ²	Food sample survey
	Water	Sediment	Soil	Air				
Number of measured chemicals	61	61	9	38	12	61	41	13

Materials for the Commission on Endocrine disruptors held during 1999 ~ 2004 and results of POPs monitoring surveys during 2002 ~ 2003

¹ **Fish:** greenling, ayu, butterfish, Japanese dace, rock greenling, common minnow, large-mouth bass, scorpion fish, dark chub, silver crucian carp, koi (carp), salmon, saury, white croaker, Japanese sea bass, Japanese sea bass (young), tilapia, skin carp, rainbow trout, goby, , Japanese dace (young), crucian carp, bluegill, striped mullet, common brackish goby, common crucian carp, far eastern dace, southern black sea bream, stone moroko, pond smelt; **Shellfish:** Japanese mussel, mussel, Japanese deck mussel, freshwater clam (Species measured differ in each year)
² **Mammals:** Japanese field mouse, Himalayan bear, raccoon dog, Japanese macaque, brown bear, harbor seal, ringed seal, stejneger's beaked whale, melon-headed whale, spectacled dolphin, blainville's beaked whale, Indian porpoise, fin whales, porpoise, hubbs' beaked whale, common dolphin, mink whale; **Birds:** brown hawk owl, golden eagle, black-tailed gull, ezo owl, Screech Owl, goshawk, Common Cormorant, Common Cormorant eggs, short-eared owl, white owl, hawk eagle, hawk eagle eggs, Eastern Marsh Harrier, kestrel, *Accipiter virgatus*, pigeon, kite, buzzard, vulture, shrike, falcon, falcon eggs, owl, owl eggs, osprey, gray starling; **Amphibians:** Tokyo potbellied frog, leopard frog, Japanese red frog, mountain red frog (Species measured differ in each year)

(2) Tests Using Fish to Assess the Effects on Ecosystems

Based on the list in SPEED '98, literature on the endocrine disrupting effects on wild animals and aquatic organisms as well as literature on *in vitro* testing were searched and collected for each chemical, and the reliability of them were assessed by experts. Based on the results of literature search, chemicals to be tested were selected and vitellogenin assay³ and partial life cycle test⁴ were conducted using medaka. As necessary, full life cycle test⁵ was added. For the specification of the test concentrations (Figure 1), the concentrations in the environment, existing toxicity data and information on the nature of each chemical was considered.

The tests were conducted for 28 chemical and it was postulated that 4-Nonylphenol (branched form) and 4-t-Octylphenol have a strong endocrine disrupting effect on medaka at the concentrations believed to be present in the environment in Japan, and that Bisphenol A also has an endocrine disrupting effect on medaka. For the remaining 23 chemicals, it was determined that no clear endocrine disrupting effect could be recognized (as of December 2004, full life cycle tests were underway for o,p'-DDT and p,p'-DDE). The test results are summarized in Table 2.

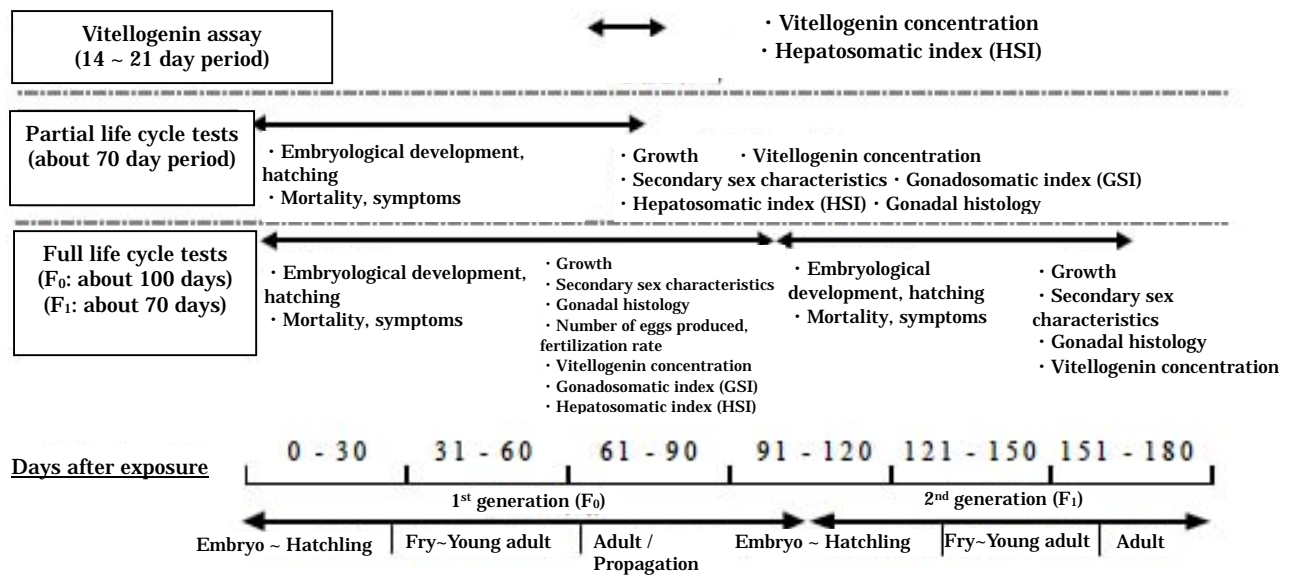
Assessments of the endocrine disrupting effects were made based on the above-mentioned series of tests using medaka, but it has been pointed out that even for medaka, for which there has been significant accumulation of basic knowledge as a test animal, it is necessary to gather relevant information in order to further evaluate the results, and that there are issues relating to improving the efficiency, such as shortening the test period.

There have also been vitellogenin assay using *Xenopus laevis*, a sex-transformation test using Japanese quail, and an enhanced OECD test method using *Daphnia magna*. (Appendix (4))

³ Vitellogenin assay: Vitellogenin is a protein unique to the female that is a component of egg yolk, and absorbed by the oocytes during vitellogenesis. For this assay, the appearance of vitellogenin in the body of the males is observed. This is thought to be one indicator for endocrine disruption. Male medaka is exposed to a test substance for a 21-day period.

⁴ Partial life cycle test: Observation of the effects on gonadal histology etc. by exposing medaka to a test substance throughout the growth period starting from the fertilization stage.

⁵ Full life cycle test: Observations to grasp the effects throughout the entire lifespan by exposing Medaka to a test substance for at least two generations.



The exposure to the test substance is 21 days to male medaka for the vitellogenin assay, about 70 days throughout the growth period starting from fertilization for the partial life cycle test, and at least two generations (about 180 days) for the full life cycle tests. For medaka, the period from hatching to spawning is about 90 to 120 days.

Figure 1 Medaka test outline

Table 2 Results of tests using Medaka

name of chemicals	Test results
Di-2-Ethylhexyl adipate	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
Amitrole	Clear endocrine disrupting effects were not recognized.
Triphenyltin chloride	Clear endocrine disrupting effects were not recognized.
Tributyltin chloride	Clear endocrine disrupting effects were not recognized.
Octachlorostyrene	Clear endocrine disrupting effects were not recognized.
4-t-Octylphenol	(1) strong binding to the fish female hormone receptors, (2) elevated vitellogenin (egg yolk protein precursor) concentration in the liver, (3) emergence of testis-ova, (4) the number of eggs produced and the fertilization rate were both low. It is postulated that there is a strong endocrine disrupting effect on fish.
cis-Chlordane	Clear endocrine disrupting effects were not recognized.
2,4-Dichlorophenol	Clear endocrine disrupting effects were not recognized.
4-Nitrotoluene	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
trans-Nonachlor	Clear endocrine disrupting effects were not recognized.
4-Nonylphenol (branched)	(1) strong binding to the fish female hormone receptors, (2) elevated vitellogenin (egg yolk protein precursor) concentration in the liver, (3) emergence of testis-ova, (4) the fertilization rate is low. It is postulated that there is a strong endocrine disrupting effect on fish.
Bisphenol A	(1) binding to the fish female hormone receptors, although weak, was recognized (2) elevated vitellogenin (egg yolk protein precursor) concentration in the liver, (3) emergence of testis-ova, (4) higher number of days of incubation (delayed hatching). It is postulated that there is an endocrine disrupting effect on fish.
Diethyl phthalate	Clear endocrine disrupting effects were not recognized.
Di-2-ethylhexyl phthalate	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
Dicyclohexyl phthalate	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
Di-n-butyl phthalate	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
Dipropyl phthalate	Clear endocrine disrupting effects were not recognized.
Dihexyl phthalate	Clear endocrine disrupting effects were not recognized.
Dipentyl phthalate	Clear endocrine disrupting effects were not recognized.
Butylbenzyl phthalate	Clear endocrine disrupting effects were not recognized.
β -Hexachlorocyclohexane	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
Hexachlorobenzene	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
Benzophenone	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized for low concentrations (comparatively low concentration considered for the fish estimated exposure dose obtained from literature).
Pentachlorophenol	Clear endocrine disrupting effects were not recognized.
p,p'-DDD	Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized.
p,p'-DDE	Since elevated vitellogenin (egg yolk protein precursor) concentration in the liver and a concentration-dependent emergence of testis-ova were recognized, the assessment is planned after the completion of full life cycle testing
o,p'-DDT	Since elevated vitellogenin (egg yolk protein precursor) concentration in the liver and a concentration-dependent emergence of testis-ova were recognized, the assessment is planned after the completion of full life cycle testing
p,p'-DDT	Clear endocrine disrupting effects were not recognized.

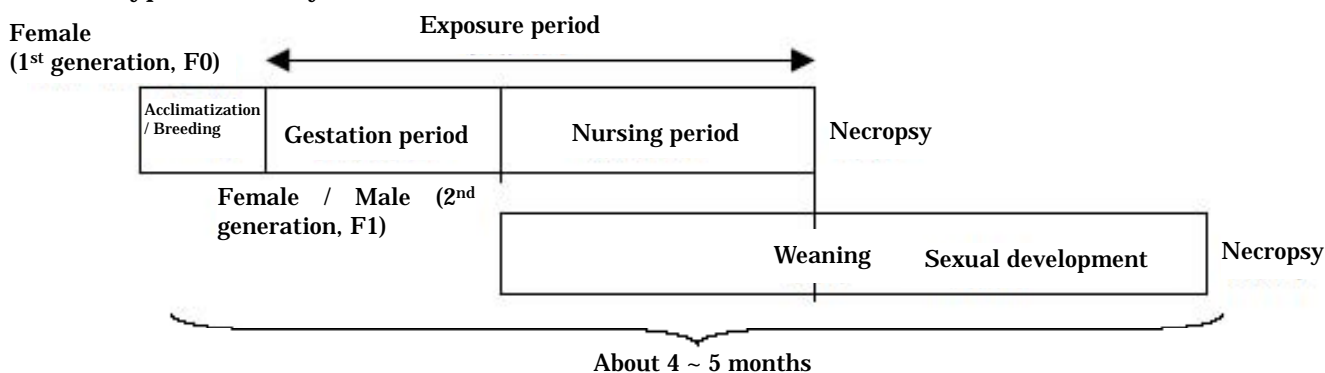
(3) Tests Using Mammals and Epidemiological Surveys to Assess the Effects on Human Health

Tests Using Mammals

An enhanced one-generation test using rats (Figure 2) was developed, and based on the list in SPEED '98, literature on the endocrine disrupting effects on mammals as well as literature on *in vitro* testing were searched and collected for each chemical, and the reliability of them was assessed⁶ by experts. Tests were conducted using the test chemicals selected based on the results of literature-search. The test doses and endpoint were selected based on consideration of the environmental concentrations of the test chemicals, the estimated exposure doses to humans, existing toxicity data and information on the nature of each chemical. For the specification of the test doses, the goal was set to detect any reactions from a dose to which a human was likely to be exposed and also non-dose correlated reactions. The purpose was not that of conventional risk assessments. In principle, there were four groups receiving doses considered to be the estimated human exposure doses, and one group receiving a dose already reported to be associated with some kind of hazardous effects. The results were assessed with reference to test results from the uterotrophic test⁷, Hershberger assays⁸, and the enhanced 28-day repeated dose toxicity test conducted mainly by the Ministry of Economy, Trade and Industry⁹.

Tests were conducted for 28 chemicals using rats. It was determined that none of these chemicals showed clear endocrine disrupting effect at the doses considered to be the estimated human exposure doses. The test results are summarized in Table 3.

Since these were tests using animals, the tests were done in the presence of that could not be completely eliminated from the diet, nor could be quantitatively controlled (for example, phytoestrogen(plant-derived substances with estrogen like effects) and phthalate esters). Since it is not practically possible to establish a control group with a zero exposure dose of endocrine disruptors, it was clear that there is a limit for understanding precise variation over the dose levels considered to be the estimated human exposure doses. In the future, it is necessary to investigate not only at the possible human exposure doses, but also at dose levels that consider the various types of toxicity assessments and methods.



The gestation period of rats is about 22 days, and about 21 days from birth until weaning. The time from weaning until pregnancy is possible is about 30 ~ 35 days. For males, it takes about 40 days for separation of the prepuce. Exposure to the test substance is made throughout the gestation period until weaning, about 43 days.

Figure 2 Enhanced one-generation rat test outline

⁶ Materials for the Commission on Endocrine Disruptors held during 2000 ~ 2004 (in Japanese).

⁷ Uterotrophic test: Immature female rats or female rats with the ovaries removed are dosed with the test substance, and the estrogen-like effects are assessed from changes in the weight of the uteri.

⁸ Hershberger assay: Immature male rats or male rats with the testicles removed are dosed with the test substance, and the androgen effects are assessed from prostate weight and examinations of secondary sex glands.

⁹ Enhanced 28-day repeated dose toxicity test: The subject is dosed with the test substance for a 28 day period, and indicators related to endocrine disruption, including genital morphology, sperm formation, and serum hormone concentrations, are assessed.

Table 3 Results of enhanced one-generation test using rat

name of chemicals	Test Results
Di-2-Ethylhexyl adipate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Amitrole	Clear endocrine disrupting effects were not recognized for doses (3 dose groups) believed to be likely human exposure doses obtained from literature.
Triphenyltin chloride	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Tributyltin chloride	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Octachlorostyrene	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
4-t-Octylphenol	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
cis-Chlordane	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
2,4-Dichlorophenol	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
4-Nitrotoluene	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
trans-Nonachlor	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
4-Nonylphenol (branched)	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Bisphenol A	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Diethyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Di-2-ethylhexyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Dicyclohexyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Di-n-butyl phthalate	Clear endocrine disrupting effects were not recognized for doses (5 dose groups) believed to be likely human exposure doses obtained from literature.
Dipropyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Dihexyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Dipentyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Butylbenzyl phthalate	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
β -Hexachlorocyclohexane	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Hexachlorobenzene	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
Benzophenone	Clear endocrine disrupting effects were not recognized for doses (3 dose groups) believed to be likely human exposure doses obtained from literature.
Pentachlorophenol	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
p,p'-DDD	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
p,p'-DDE	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
o,p'-DDT	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.
p,p'-DDT	Clear endocrine disrupting effects were not recognized for doses (4 dose groups) believed to be likely human exposure doses obtained from literature.

<http://www.env.go.jp/chemi/end/speed98/speed98-19.pdf>

Epidemiological Survey

For the investigation of effects on humans, there are epidemiological methods in addition to the tests using mammals.

Surveys and studies on exposure to chemicals such as Dioxins using human umbilical cords and surveys on the prevalence of congenital abnormalities have been conducted, so that some understanding of the exposure situation has been obtained.

There have also been studies on sex ratios at birth, the effects on urogenital organs, as well as research on human testis weights and sperm formation, but these have not extended to an assessment of phenomena which raise concerns about effects on human health.

It is difficult to implement epidemiological surveys that enable assessment of the relationships between exposure in the environment and suspected health effects. (Tables 4-1 and 4-2)

Table 4-1 Outline of epidemiological surveys (1)

	Outline	Results
Survey of human congenital abnormalities	It has been pointed out that endocrine disruptors may contribute to the occurrence of congenital abnormalities in humans through the disruption of the endocrine system. Therefore concentrations of Bisphenol A and Nonylphenol in the umbilical cord blood and in the blood of human females, both during pregnancy and while not pregnant, were measured in order to understand the relationship between Bisphenol A, etc. and the occurrence of congenital abnormalities. There have also been measurements of the serum concentrations of the two mentioned substances of infants with hypospadias and their mothers (while not pregnant).	It was not possible to form a conclusion about a causal relationship between the concentration of chemicals in the blood or umbilical cord blood and the occurrence of hypospadias.
Surveys and studies on exposure to chemicals, such as Dioxins using human umbilical cords	There is concern that fetuses are highly sensitive to chemicals, but detailed investigations on fetal exposure to chemicals have not been conducted. There have been surveys on detection rates and concentrations in the umbilical cord, umbilical cord blood, and the mother's blood for dioxins, PCBs, organic chlorides, estrogens, and phytoestrogens.	Dioxins, PCBs, DDTs, hexachlorobenzene (HCB), hexachlorohexane (HCH), Endosulfan, Chlordane, and phytoestrogens (Genistein, Daidzein, Equol) were detected in more than 80% of the survey subjects. Aldrin and Endrin were not detected. Results of preliminary tests show that Bisphenol A, phthalate esters and heavy metals were also detected. There was shown to be a correlation between the total PCB concentration in the mother's blood and the concentrations in the umbilical cord and the umbilical cord blood. However, there was no apparent correlation with PCB congeners/isomers. The concentrations of phytoestrogens, Genistein and Daidzein tended to be higher in the umbilical cord blood than in the mother's blood. It is necessary to investigate the relationship between chemical concentrations and the age of the mother (or age at delivery).

Materials for the Commission on Endocrine Disruptors held in 2004(First and Second)

Table 4-2 Outline of epidemiological surveys (2)

	Outline	Results
Survey of sex ratios at birth	As there was a report of a decline in the percentage of males among infants born in the Kasumigaura region ¹⁰ , a survey was conducted on sex ratios nationally and around Kasumigaura.	There was no clear change in the sex ratios observed in the area around Kasumigaura.
Survey of effects on urogenital organs.	Since it was pointed out that endocrine disruptors may contribute to reproductive function abnormalities in humans, a survey of reproductive function in young males was conducted on groups of college students. A national survey was conducted on cryptorchidism in male children under the age of 3 years. A survey on the frequency of testicular cancer was also conducted.	For the survey of reproductive function, there was no clear result obtained. For the cryptorchidism, there were no apparent peculiarities in patients or parents regarding pregnancy history, birth measurements, parent's diet, medication or occupation. It was thought that the probability of effects from environmental factors, including exposure to endocrine disruptors, is extremely low. With regard to the frequency of testicular cancer, although there is a gradual increase in the number of cases, it does not constitute evidence of a connection to chemicals.
Research on human testicular weight and spermatogenesis	There is concern about reduced sperm counts and reduced testicle size in men. Investigation of testicle weight and testicular tissue was performed by analyzing autopsy records of abnormal corpses at the Tokyo Medical Examiner's Office	Sorted by age at the time of death (from 20s to 60s), height increased in each age group for more recent birth dates. With regard to testicular weight, however, there was no linear increase, even for more recent birth dates. The results of the investigation of testicle weight by age at the time of death in 5-year groupings indicated a tendency for testicle weight to reach the maximum value at a younger age as the subject group becomes of more recent birth. A relationship between testicle weight and sperm production was observed. With regard to a relationship between testicle weight and cause of death, there was a tendency for low testicle weight for cases of death due to malnutrition, and higher testicle weight associated with instances of sudden death. Data on normal, healthy adults were not obtained.

Materials for the Commission on Endocrine Disruptors held in 2004(First and Second)

¹⁰ Mizuno, Reiko (2000) Decline in birth rates of male infants in the Kasumigaura basin and Tonegawa estuary. Kagaku, 70:113-118 (in Japanese)

(4) International Activities

There are many issues to be solved concerning endocrine disruptors, including clarification of the mechanisms and the causal relationship with exposure, and development of test methods. It is important to advance research and study under international collaboration and cooperation.

MOE has been conducting an annual International Symposium on Endocrine Disruptors since 1998. In addition, joint research projects are being conducted with UK and the Republic of Korea. There is also active cooperation with international agencies such as OECD and WHO. (Table 5)

Table 5 Outline of international activities

International symposium on Endocrine Disruptors	These were held in Tokyo 1998, Kobe 1999, Yokohama 2000, Tsukuba 2001, Hiroshima 2002, Sendai 2003 and Nagoya 2004. Each symposium runs for 3 days. The first day is a presentation of information on the status of domestic and international activity as a program for the general public. The second and third days are programs for experts, with presentations of the latest research by foreign researchers and discussions of future directions. So far about 10,000 people have participated, including 500 participants from abroad.(http://www.env.go.jp/chemi/end/index3.html)
Bilateral research projects	Bilateral collaborative workshops have been held in order to exchange technical data, conduct joint research and provide interaction among experts. Specific themes cover a broad range, from basic research on genetic cloning and identification of hormone receptors to monitoring of effect of endocrine disruption on the native species of each country. Bilateral research has been underway since 1999 with UK, and since 2001 with the Republic of Korea. In 2004 a bilateral collaboration with the USA was started to share information on test method development. (Materials for the Commission on Endocrine Disruptors held in 2004)
Cooperation with the Organization for Economic Cooperation and Development (OECD)	Some of the test methods developed in Japan have been proposed to the OECD as international standard test methods (an invertebrate test method 'enhanced TG211', a bird test method 'enhanced TG206'). In addition, Japan actively participates in test method validation work on fish and frogs screening methods being advanced by the OECD (http://www.oecd.org/home)
Cooperation with the World Health Organization (WHO)	WHO/ILO/UNEP issued the WHO Global Assessment in 2002 summarizing the latest scientific information on endocrine disruptors. MOE participated in preparing this summary, and translated the WHO Global Assessment into Japanese. This Japanese translation (MOE version) is accessible on MOE website.(http://www.env.go.jp/chemi/end/index4.html)

II. Future Direction

1. Basic Concepts

The origin of the focus on endocrine disrupting effects was the suggestion of a connection between reproductive abnormalities in wildlife and an exposure to substances with hormone-like effects. However, the understanding of abnormalities in wildlife is not the only issue for endocrine disruptors, it is also the starting point for countermeasures for chemicals in view of the protection of the ecosystem.

Conventionally, the effect of a chemical on the ecosystem, which is related to many factors, is difficult to prove directly through laboratory experiments. For this reason, it is necessary to first continuously observe wildlife in the nation, determine whether the observed phenomena are normal or abnormal through scientific surveys, and understand the variations of individual organisms (groups). Next, there should be an estimate of the effects on the ecosystem based on these results. It is also necessary to collect basic biological knowledge and learn more about the interrelationships between species in order to assess whether observed phenomena are normal or abnormal. Also for the estimation of the effects on the ecosystem, essential is basic biological knowledge.

When investigating the effects of endocrine disruptors on the ecosystem, there is also a need for continuous observation and accumulation of basic biological knowledge. In particular, it is necessary to make progress on collecting the basic knowledge on the endocrine systems of each species and on the basic research on the various mechanism of endocrine disruption. In order to understand the effects of substances in the environment on the ecosystem and the human health, it is necessary to understand concentrations of substances in the environment and whether there is exposure. As is already known, there are natural hormone-like substances (phytoestrogens and hormones derived from humans and animals). In order to grasp the situation in the environment, it is necessary to also consider the exposure to these substances.

In addition to the effects via hormone receptors, it has been pointed out that endocrine disruption can also occur through metabolic processes without affecting receptor-binding processes. It has also been pointed out that in addition to changes that are apparent during the development of an individual organism, there is also possibility that latent effects received during the development process will become apparent later in the adult stage. Endocrine disruption is an important topic of research, but for measures against chemicals in general it is important to gain a comprehensive understanding of the various hazardous effects of chemicals on living organisms.

In addition to the basic and fundamental research mentioned above, it is also important to establish a variety of test assessment methods in order to estimate the effects on the human health and on the ecosystem using the knowledge MOE has at the moment. In the studies so far, there have been no chemicals found to have endocrine disrupting effects on rats at doses corresponding to concentrations in the environment. For medaka, however, some chemicals have been found to

possess endocrine disrupting effects at concentrations in the environment. According to the agreement on the inter-ministerial cooperation on endocrine disruption, the main focus of MOE is environmental protection. To accomplish this, it is considered important to establish test methods for the assessment of effects on the ecosystem, and to focus on the implementation of tests. MOE will continue to actively cooperate in the establishment of test methods being advanced by the OECD, etc., and work to make positive contributions internationally.

As measures to handle chemicals in general, it is necessary to perform comprehensive risk assessments based on the exposure situations, and to link this to risk management, based on the data obtained from the perspective of assessing the hazards from a variety of viewpoints, not only the data on endocrine disruption.

Much of the information related to chemicals requires effort to fully understand, including scientific details. Furthermore, since there are still many uncertainties regarding endocrine disrupting effects, in order to avoid irrational anxiety, it is extremely important to provide accurate information and promote risk communication based on accurate understanding and shared knowledge.

From this perspective, the following will be promoted as the foundations of the activities to deal with the endocrine disruptor problem: (1) Observation of wildlife, (2) Evaluation of the environmental concentrations and exposure level, (3) Promotion of basic research, (4) Effects assessment, (5) Risk assessment, (6) Risk management, and (7) Promotion of information sharing and risk communication.

The issues indicated internationally have been compared with the items already handled by MOE to identify and classify specific issues for the future. References used for the comparison include the WHO Global Assessment¹¹, WHO workshop reports¹², IUPAC reports¹³, and EC strategies on endocrine disruptors¹⁴.

¹¹ WHO (2002) Global assessment of the state-of-the-science of endocrine disruptors, WHO/IPCS/EDC/02.2.

¹² WHO/UNEP/ILO (2004) Report of the joint IPCS-Japan workshop on "Endocrine disruptors: Research needs and future directions", WHO/IPCS/EDC/01/04.

¹³ J. Miyamoto and J. Burger (2003) Implication of Endocrine Active Substances for Human and Wildlife, Scope/IUPAC.

¹⁴ EC (2001) Communication from the Commission to the Council and the European Parliament on the implementation of the Community Strategy for Endocrine Disruptors- A range of substances suspected of interfering with the hormone systems of humans and wildlife (COM(1999)706) , COM(2001)262 final.

2. Specific Objectives

(1) Observation of Wildlife

Reproductive abnormalities in wildlife in various regions throughout the world had been observed, and it had been suggested that there would be a connection to exposure to chemicals. Especially endocrine disruption was pointed out as the causative mechanism. (Page 16, Note 11) As a result, surveys were being made on the effects of chemical exposure on wildlife in various regions all over the world. Examples in Japan of possible causal relationships between abnormalities in wildlife and exposure and/or accumulation of substances (including natural and synthetic hormones) in organisms, include reproductive organ abnormalities observed in female rock shell (*Thais clavigera*), and elevated vitellogenin concentrations in the blood of male koi (Page 6), but there have not been many reports on wildlife abnormalities.

Finding abnormalities in wildlife is the starting point for measures against chemicals for the ecosystem, not just for the endocrine disruptor problem.

It is important to contribute to the preservation of the environments, which is irreplaceable, and efforts are required to grasp changes and precursory phenomena along with time-course in wildlife. It is necessary to continue to build a scientific monitoring system of the ecosystem with experts, but there is a limit to the activities of them. Observation at the local level by children and ordinary citizens can enable them to gain knowledge to determine whether changes in the ecosystem are one of the nature variations there and can be developed into the more detailed studies by a limited number of specialists.

Specific examples that can be started at the present time are presented below.

Continuous observation of wildlife at the local level

For the continuous monitoring of wildlife in the community, it is desirable to make use of the observation activities of local citizens and the nature observation training conducted at schools in various regions. This kind of activity is steady and continuous monitoring rooted in the local region. Although there are limits to the precision and identification of species due to lack of involvements of specialists, it is believed to be invaluable for obtaining an understanding of the current status of the ecosystem, including the various types of wildlife. By creating networks of local schools and existing activities, and collecting a standardized level of information, such as the species to be observed, the items to be reported and the location of the surveys, it will be possible to contribute to selection of fields, etc. for the studies by experts.

In addition, the participation of children and ordinary citizens in the observation of wildlife is expected to nurture interest and concern for the ecosystem, and enable people to learn the diversity of the ecosystem.

As the first species for common observation, aquatic organisms have the advantage of having easily-identifiable habitats. It is currently planned to start with medaka, for which test methods on endocrine disrupting effects have been developed, and later add target species to achieve

comprehensive monitoring.

Survey and evaluation by experts

Starting with observation data from the local level, a limited number of experts can utilize those data and extend their fields nationwide. In the case that experts suspect significant changes from field surveys, more detailed studies should be conducted through examination of specimens captured for pathological examination, if possible, or based on the observation details, such as measurements of the concentrations of various substances in the habitats, studies using biomarkers to investigate sources of variation and teratogenicity, hybridization experiments between abnormal organisms or between abnormal and normal organisms, or studies of possible causes other than chemicals, such as radiation. (Figure 3)

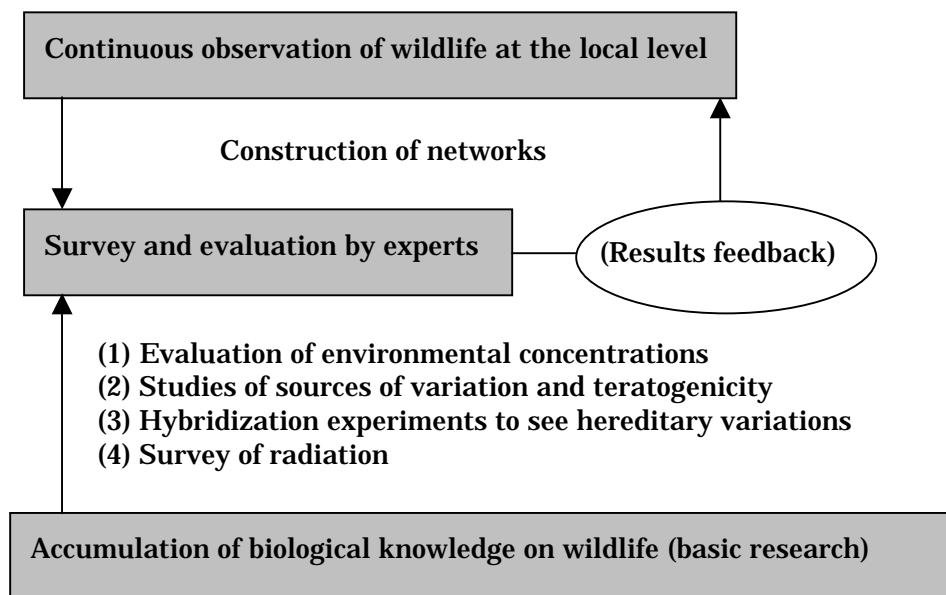


Figure 3 Conceptual diagram of observation of wildlife and comprehensive surveys

(2) Evaluation of the Environmental Concentrations and Exposure Level

In order to properly assess the environmental risk of chemicals, it is crucial to understand the existing concentrations in the environment, as well as data related to the hazard. Therefore, since 1998, environmental surveys have been underway to determine the levels of the chemicals listed in SPEED '98. Environmental survey and wildlife monitoring of chemicals (called "black book reports", because the reports have black covers) have been conducted since 1973, presenting the presence of chemicals in the environment using samples from a variety of media, including water, soil and air etc.. However, there are tens of thousands of chemicals present in the environment, and there is a limit to the survey and analysis capabilities.

In the future, the selection of substances for the black book reports will include consideration of endocrine disrupting effects. In addition, natural substances, such as phytoestrogens (plant-derived estrogens) will be also considered in the selection process. Using the limited survey and analysis capabilities to the utmost, it is desirable to maintain a constant and nationwide understanding of the environmental situation and to make broad, effective use of the results obtained for various countermeasures for chemicals, including measures against endocrine disruptors. (Figure 4)

Environmental survey and wildlife monitoring of substances

i) Preliminary environmental survey

For substances for which the presence in the environment is not clear, conduct surveys with the primary goal of verifying the presence.

ii) Detailed environmental survey

For substances confirmed to be present in the environment, make quantitative measurements using advanced analysis methods for each environmental medium, water, soil and air.

iii) Monitoring survey

For chemicals which require knowledge about residual amounts in the environment over time, because of accumulation in organisms or persistence in the environment, conduct regularly scheduled surveys using advanced analysis methods. If there is a switch to a higher-sensitivity analysis method, conduct the high-sensitivity analysis on samples from past surveys in order to maintain the data comparability over time.

iv) Exposure level survey

Gain an understanding of the exposure levels through exposure routes via media like foods and indoor air. Verify the accumulated quantities within the bodies of wildlife.

v) Human sample survey

As part of the effort to understand exposure levels, measure substance concentrations in body samples, specifically, human blood and human umbilical cord blood etc..

Estimation of concentration levels of substances in the environment

Starting with specific rivers and regions, create and verify estimation models using basic data

obtained through actual measurement in order to simplify the process to detect detailed changes in the concentrations of substances, and to estimate changes in concentration levels in specific areas.

Environmental sample preservation

Since it is likely that the substances that will be the target of study will change, and that analysis methods will advance, a portion of the samples used in the surveys will be placed in freezing storage to enable re-analysis in the future.

Development of more sensitive analysis methods

For the selection of analysis methods, in addition to reproducibility, convenience, and cost considerations, it is also necessary that the methods satisfy the required sensitivity. For substances for which the existing analysis methods do not satisfy the sensitivity required for risk assessment, promote the development of high-sensitivity analysis methods to enable analysis of the concentrations present in the environment and contribute to the accurate understanding and assessment of exposure levels.

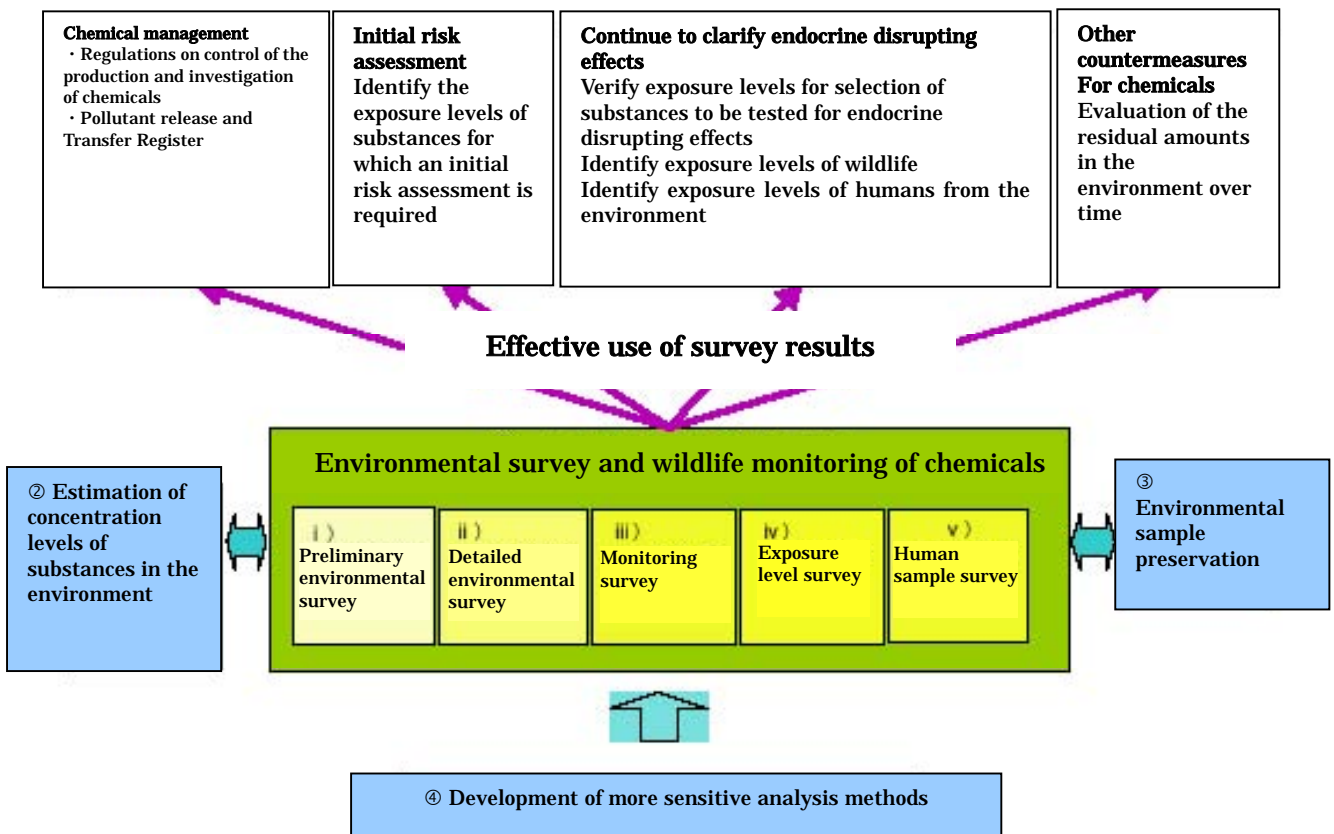


Figure 4 The structure of environmental survey and wildlife monitoring of substances

(3) Promotion of Basic Research

Compared to the situation in 1998, there is now a considerable accumulation of knowledge on endocrine disruption. However, there are still many issues to be resolved.

Understanding abnormalities of wildlife is not only an issue of endocrine disruptors, it is also important as a starting point for measures against chemicals from the viewpoint of preservation of the ecosystem. When changes in wildlife are observed, it should be determined, based on basic biological knowledge, whether the observed phenomenon is an abnormality of the organism (group) or not and what are the causes and mechanisms of the abnormality. And if there is a suggestion of relationship between changes and chemicals, investigations should be conducted including the evaluation of the involvement of endocrine disruption.

In order to ascertain whether an observed phenomenon is a direct effect of endocrine disruption or a secondary effect via endocrine disruption, knowledge on the mechanisms is indispensable. It is also necessary to clarify the relationships between hazardous effects on an individual level and changes on the cellular/molecular level.

Furthermore, it is necessary to establish a variety of test methods to estimate the impact on the ecosystem and the human health using the knowledge that is currently available. As for the development of test methods using fish and amphibians, it is important to continue to actively participate in the OECD activities. Figure 5 shows a feasible framework for basic research.

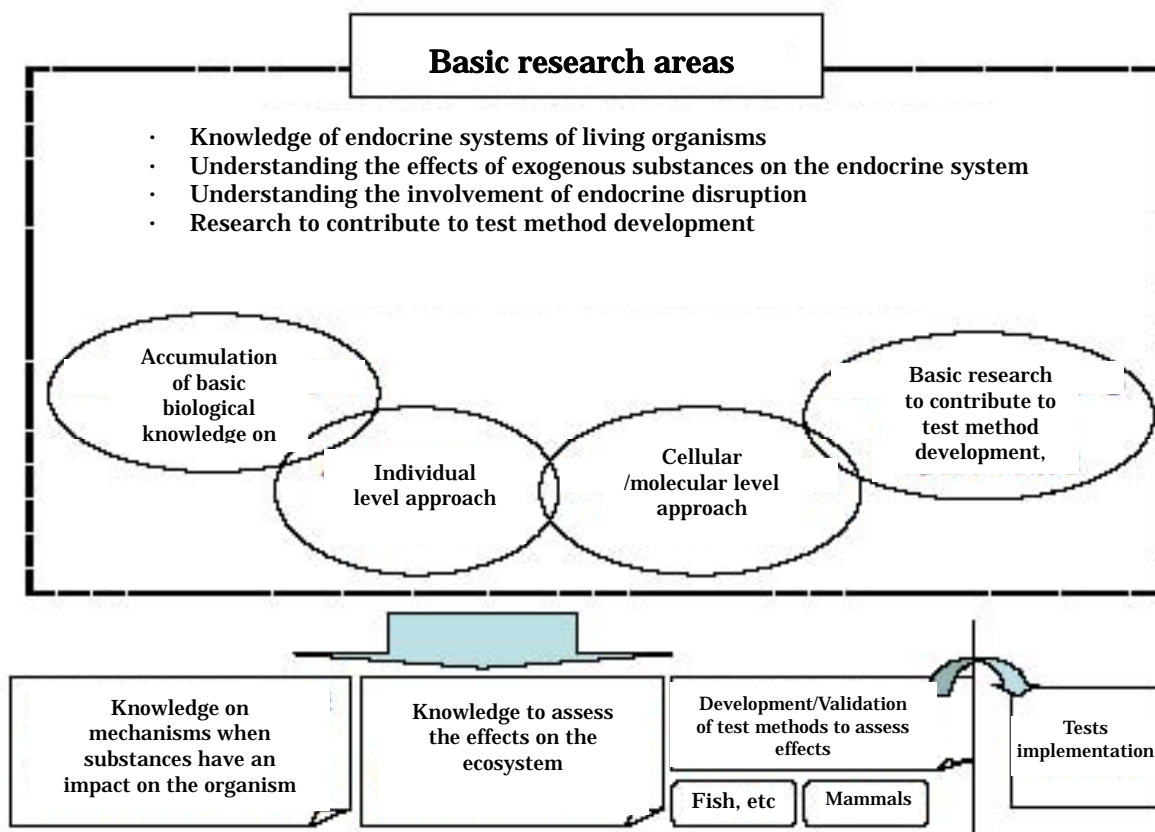


Figure 5 Basic research on endocrine disrupting effects of substances

Accumulation of basic biological knowledge of wildlife

When changes or precursory changes are detected on an organism (or a group) through observation of wildlife, it is important to assess whether the change is abnormal or not, and to understand the mechanism of the change. To do this, it is necessary to have basic biological

knowledge of the species. Furthermore, when it is determined to be an abnormality, it is necessary to analyze the causes. This means, in addition to the measurement of concentrations of various substances in the habitat of the observation, it is required to accumulate information on the factors on the living organisms' side, that is, the factors regulating the differences in sensitivity relative to exposure to substances. Furthermore, an understanding of the environmental factors having an impact on the organism (such as physical factors of the environment, like changes in sunlight, temperature, and radiation) is not negligible. It is essential to continue to advance studies corresponding to the observed details.

Individual level approach

The advantages of the individual level approaches, like *in vivo* experiments, are the ability to evaluate the absorption, distribution in the body, metabolism, and excretion of chemicals, the ability to comprehensively assess the entire endocrine system as well as other toxicity evaluation items, the ability to assess a wide range of mechanisms, and the historical evidence that toxicity tests at the individual level have been used for decades.¹⁵

It is necessary to investigate epidemiological methods that enable investigation of the causal relationship between human health effects at the individual level and exposure to substances in terms of endocrine disrupting effects.

i) Investigation of the dynamics of substances in the body

Investigation of the processes involving a substance in the body, including absorption, the distribution in the organs, metabolism, and excretion.

ii) Effects on organs and functions other than reproductive systems and effects on the endocrine system as a whole

For the assessment of the endocrine disrupting effects of a substance, basic knowledge based on a comprehensive understanding of biology will be collected, including the effects on target organs of the endocrine system other than the reproductive system, such as the thyroid and pituitary gland, as well as on non-endocrine/reproductive system effects, including effects on the nervous system and immune systems. It is also important to obtain the basic knowledge to evaluate and measure the effects between normal reactions and adverse reactions.

Cellular/molecular level approach

The advantages of cellular/molecular level approaches, like *in vitro* experiments, are the efficiency and practicality of the testing (low cost, automation, short time periods), and that the information obtained contributes to the understanding of the specific mechanisms.¹⁵

i) Development of DNA micro-array

Recently, along with the progress in genomic technologies and the structural and functional studies of proteins, it has become possible to conduct a variety of investigations to assess the mechanisms of substances with data obtained using genomic technology. For example, in

¹⁵ USEPA(1998)Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) Final Report

toxicogenomics, which uses genome analysis techniques for toxicological assessments, a technology called the DNA micro-array is receiving a great deal of attention. The micro-array is characterized by the ability to comprehensively analyze the expression of multiple genes, and is a ground-breaking technology for clarifying the expression of hazardous effects at the genetic level.

However, the technology at the present stage is not necessarily sufficient in terms of quantification, reproducibility and sensitivity, so it is still not adequate to use this technique for analyzing the roles of multiple genes showing expression changes within an organism. Furthermore, it is not sufficient for analyzing the significance of genetic changes over time, or the effects of long-term exposure. At the present stage, it is most often used as a screening technique for genes (groups) of interest. It may become a valuable technology in the future, and application development as a technology for impact assessment is expected.

Furthermore, in order to properly assess the effect of a variety of substances, it is necessary to clearly identify the effects within the body for key species, such as medaka.

It is desirable to construct a database of the information on gene expression changes obtained using micro-arrays, and allow public access as far as reasonably possible.

ii) Identification of receptors and signal transmission systems

It is expected to identify the receptors that could be one effect point of substances, as well as the connected signal pathways, analyze the structure and expression of the receptors, and clone the relevant genes.

iii) Dynamics of receptors and transcription factors

It is necessary to clarify the sequences of mechanisms at the cellular/molecular level, including the binding of substances to receptors, and the turning ON/OFF of genes mediated by the subsequent activity/non-activity of the transcription factors.

iv) Investigation of whole organism control mechanisms not mediated by receptors

It is desirable to investigate mechanisms that contribute to metabolic effects, at the steroid hormone synthesis stage, without effecting the binding process.

v) Assessment of effects on the cellular/molecular level

When changes at the cellular/molecular level are observed, it is necessary to clarify what kinds phenotype could be observed at the individual level. On the other hand, when changes are observed at the individual level, it is important to understand the mechanisms and assess the changes at the cellular/molecular level.

Therefore, data obtained through cellular/molecular level approaches should be compared to the results of *in vivo* experiments. It is also anticipated that a database will be constructed to enable unification and assessment.

Basic research contributing to test methods development

i) Collection of basic data on test animals

Biological knowledge on the endocrine system of each test animal in the ecosystem is required.

This basic knowledge on the endocrine systems of various species is necessary to understand properly changes due to individual variations, species differences, breeding conditions differences, and to analyze the results. Without knowledge of the normal status, it is impossible to determine what is abnormal. Basic knowledge will be accumulated for each test animal to understand the range of variation from which a return to the original is possible through homeostasis, and also know about the genesis, development, sexual differentiation and reproduction of the test animals.

ii) Search for biomarkers

A biomarker that is already used for test methods is vitellogenin. Basic biological data and knowledge on the significance of vitellogenin production in the male is still inadequate, so further accumulation of knowledge is required.

It is also necessary to search for other highly-sensitive, highly-specific biomarkers besides vitellogenin.

iii) Investigation of relationships between *in vitro* test results and *in vivo* test results

It is important to investigate the relationship between the results of *in vivo* experiments and *in vitro* experiments, such as receptor binding tests. For example, it is necessary to investigate the correlations and commonalities between false positives/false negatives in screening assays and higher-tier tests.

iv) Development and validation of test methods

As a starting point of assessment of wide-ranging effects on the ecosystem, there is a need to develop methods to assess the endocrine disrupting effects on fish and amphibians. It is important to promote research to establish a variety of international test methods to estimate the effects on the ecosystem and effects on the human health, using knowledge that is currently available.

The OECD is currently investigating several test methods at a variety of levels. Japan has been playing a leader role in the development of test methods related to endocrine disruptors, and is expected to contribute to the validation of test methods. For special areas in the test method development, such as development of receptor binding assays, standardization of vitellogenin assays, and comparison of fish test methods using medaka, it is important to continue to build bilateral collaboration to exchange information with other countries conducting advanced research.

(4) Effects Assessment

In the beginning when the measures concerning the endocrine disruption were started, listing up and indicating the substances to be studied from the limited information available at that time, served as a great driving force in the implementation of measures. However, as a result of the development of activities, it became evident that it would be mandatory to constantly update the substances that should be tested due to the accumulation of new scientific knowledge, and it might be necessary to change the category itself of the substances. Meanwhile it was pointed out that listing up the substances that should be studied at a certain point may give a false impression that they are the very substances with defined endocrine disrupting effects. As such, it would be desirable to clarify the methodology of selecting the substances to be tested and also the assessment procedures of substances rather than listing up the substances at a specific point of time.

For this purpose, the selection and assessment procedures of substances to be tested related to the endocrine disrupting effects of substances have been summarized in Figure 6. It is important to scientifically and objectively proceed with the actual operation and the set up of detailed conditions after obtaining an informed and considerable consent in a deliberation by intellectuals in a public setting.

The selection and assessment procedures of test substances concerning the endocrine disrupting effects (Figure 6)

As for the substances that are to be considered for investigation with regards to endocrine disrupting effects, since it is difficult to grasp the whole picture of production and transaction volumes, substances that are subject to chemical-regulations, those that have been used within Japan, and those that have been suspected to have an effect on the endocrine system or to have an endocrine-mediated effect in the reports published by public agencies such as international organizations will be subject to testing. Furthermore, not only artificial chemicals but also natural substances (i.e., phytoestrogens) and human/animal derived hormones will also be considered.

Firstly, the status of detection, measurement and usage will be assessed in terms of whether there is a possibility for exposure in the general environment of Japan, and if so, in terms of its exposure level. If a possible exposure is identified, the assessment of the information on the impact and phenomena related to the endocrine disrupting effects will be carried out based on the documentary information extracted by the latest search at the time to select the test substances. If the substances to be tested have not been investigated in a similar test either inside or outside of Japan, the test should be implemented for evaluation.

After comparing the information on the level of toxic effect and/or the level confirmed with an impact by the endocrine disruption obtained through the test carried out or through a similar test in Japan and abroad with the possible exposure level in the general environment, the substances will be separated into the following categories: [Substances in which endocrine disrupting effects have been conjectured in humans in a level that is relatively close to the environment], [Substances in which endocrine disrupting effects have been conjectured in living species other than humans in a level that is relatively close to the environment], and [Substances that have been conjectured with no definite endocrine disrupting effects at this time or substances that have a very small possibility of exposure at this time that have been found with no realistic risks].

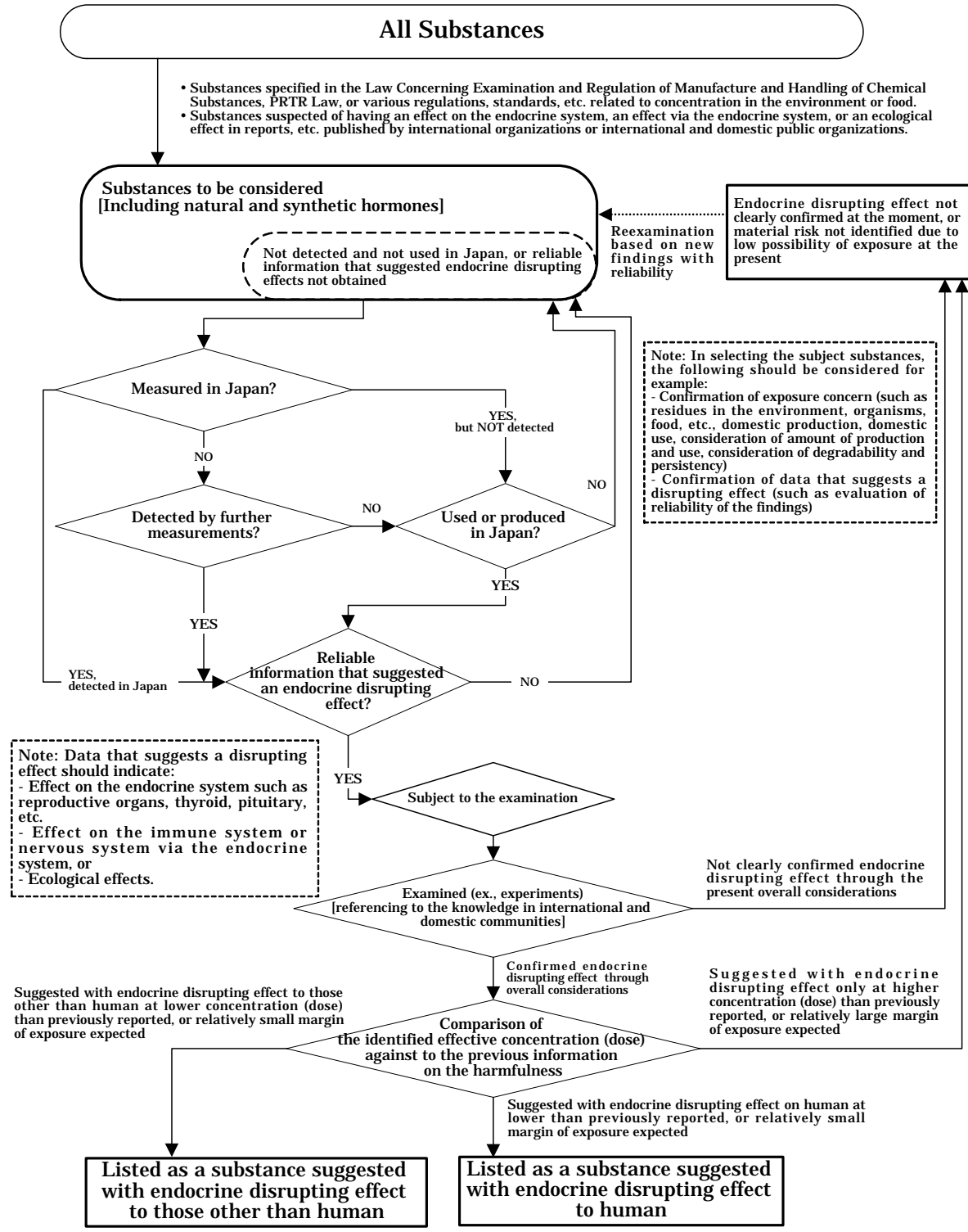


Figure 6 Flow chart for selection and evaluation of subject substances with endocrine disrupting effects

Implementation of tests

The OECD certifies various testing methods for assessing the hazards of substances as test guidelines. For a test guideline to be established, the testing method must be developed, its supporting knowledge organized and the findings accumulated by carrying out tests for actual validation. None of testing methods for endocrine disrupting effects has been established as OECD's guideline at this present stage.

Until now, MOE has actually been carrying out tests over 20 test substances by developing tests that use rats and Medaka as methods of evaluating the impact caused by the endocrine disrupters. Although the tests have not yet been led to establishment as guidelines, part of the findings and assessment of the tests have already been reported to the OECD as important information, which has enabled Japan to play the role of leading the international development of *in vivo* tests. Based on past achievements, it is important hereafter to gather knowledge through more improved methods while further accumulating supporting data.

MOE is to get involved mainly from the perspective of environmental conversation in inter-ministerial agreement on the roles of ministries. As such, MOE will be prioritizing the test that uses Medaka as a test species for assessing the effect on the ecosystem based on past achievements, focusing on investigations of the ecosystem for the foreseeable future. On the other hand, the test using rats for assessing the effect on the human health must be implemented as required, particularly if endocrine disrupting effects is suspected and exposure on humans is envisioned in view of the evaluations of the findings of tests using fish, documentary information, and the exposure level in Japan.

Until now, tests using Medaka have been carried out under the testing system with vitellogenin assay and partial life cycle test and, if necessary, full life cycle test, but in the future, an efficiency-oriented testing system will be examined anew in view of the information obtained from the tests and the required testing period for the test.

Moreover, the dosage region with a possibility of human exposure has been focused in setting up the test doses in tests using rats until now. In the future, although there is a limitation in the number of setup groups, the dosage setup could be changed allowing for information that can contribute to hazard assessment, by including not only the dosages with a possible human exposure but also those with possible adverse effects that have already been reported, by referring to various techniques of toxicity assessments.

It is advisable to secure a place for a full public discussion for analysis and evaluation of the test results.

(5) Risk Assessment

An environmental risk assessment of chemicals is for evaluating the degree of risk by carrying out two assessments; a [hazard assessment] for sorting out the dose (level) – reaction (effect) relationship by identifying the hazards on the ecosystem and human health and an [exposure assessment] for estimating the amount of exposure of the chemicals from the environment on the ecosystem and human health. (Figure 7)

In the risk assessment of chemicals, it is not appropriate to make the assessment by simply in terms of endocrine disrupting effects. This is because chemicals have various effects, and as the living organisms subjected to exposure will have various complex and associated reactions, there is a risk of producing oversight on the hazards on living organisms and misunderstandings concerning the cause and effect. The endocrine disruption must be assessed as an aspect of various effects of chemicals or as one that has been combined with other effects on living organisms.

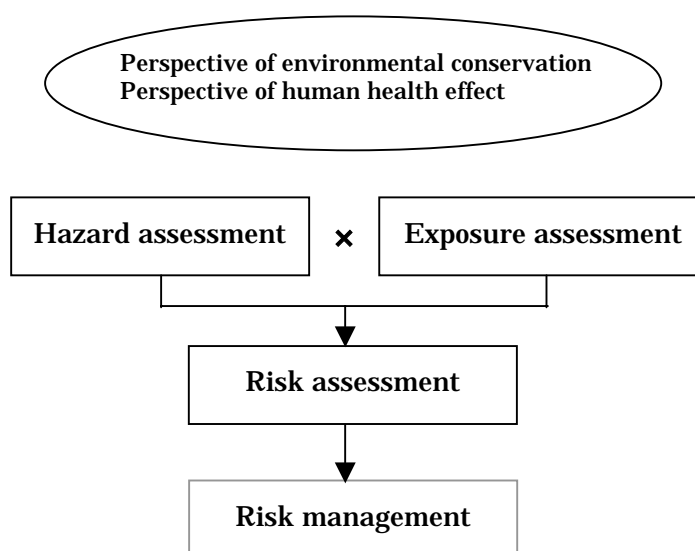


Figure 7 Conceptual diagram of Risk assessment and Risk management

(6) Risk Management

At this point, there seems to be no chemical that requires a regulatory risk management from the perspective of endocrine disrupting effects. However, depending on information accumulated in the future, it is advisable to lay out a framework that would allow for measures when required.

(7) Promotion of Information Sharing and Risk Communication

Regarding endocrine disrupting effect of substances, there are many questions still left to be answered by science, and scientific understanding requires high-level expertise. Around 1998, the issue of endocrine disruptors, regarded as a severe environmental problem, was a great public concern in Japan. There is a tendency for people not to change their attitude toward a “chemical

suspected of danger” and continue to consider it as “dangerous” even after overruling information is released to say that such once suspected chemicals have been discovered to be safe. In addition, according to some social psychologists, people’s feeling of anxiety is increased whenever they encounter something “unknown” or something “alleged to be fatal.”

In order to prevent any unverified hypothesis from increasing social anxiety, it is important for the government to promote distribution of reliable information, including messages to clarify which information is a proven fact and which is unverified theory, and also frequently update people with the latest information such as results of reliable scientific research.

Furthermore, it is necessary to promote “risk communication” between industries (suppliers) and consumers (users) so that they can make appropriate judgments on which potential environmental risks could be tolerable and which should not be accepted. Topics to be discussed for risk communication include the difficulty of completely eliminating all risks, convenience and necessity of chemicals, potential new risks and unavoidable increase of burdens on natural resources in return for introducing replacements, existence of phytoestrogens and other natural hormone-like substances, etc..

At the same time, it is hoped that environmental education for children will be promoted so that they will be able when they are grown up, to properly understand the potential risks of using chemicals, have a positive attitude toward participation in promotion of risk communication, and develop the ability to make appropriate judgments on the use of chemicals. To this end, it is important to aggressively promote distribution of reliable information and create opportunities for people to obtain the necessary information.

Information sharing

i) Sufficient provision of information

Although people’s interest in environmental risks caused by chemicals is generally high due to the direct potential impact on their living, such high interest does not necessarily lead to appropriate conduct for diminishing environmental risks in their daily life. This is due to the fact that information on chemicals requires scientific expertise and that people usually obtain only fragmentary knowledge which is insufficient for them to find a truly effective way to solve problems.

Especially, information on endocrine disruptors is quite unique and difficult to accurately understand in some aspects compared with general scientific information on chemicals. Therefore, one-way information, without any follow-ups or checkup of feedback, could most possibly make people merely confused.

Unique characteristics of information on endocrine disruptors

- It often includes a hypothesis alleged to be supported by certain results of scientific research with its credibility actually still unconfirmed among many experts. In many cases, people’s feeling of anxiety comes from unverified hypotheses. Also, “hazard” information easily

attracts people's attention and gets around quickly in many cases, while people often fail to properly understand "potential risks" even though they have been carefully determined based on comprehensive analysis of a hypothesis.

- No specific effects on mammals have been observed yet. In addition, it is impossible to draw any final conclusion to support or deny hypotheses. In some cases, people are only informed of a certain hypothesis and fail to hear any conflicting theories. Generally, once a hypothesis is widely known to the public, conflicting research results or theories to deny the hypothesis tend to be ignored.
- In many cases, people's feeling of anxiety has been simply triggered by the sudden emergence of discussions and debate on the issue of endocrine disruptors as a public concern, and such feeling tends to increase automatically.
- Many people do not know the fact that many physiological mechanisms in ecological systems of living organisms including human beings are still unknown and that the relationships between the mechanisms and respective suspected chemicals are also unknown in many aspects.

ii) Approach toward promotion of information sharing (Figure 8)

1) Updating people with the latest information utilizing internet websites

It is necessary to frequently update people with the latest information so that they may properly understand the current status and be aware that some arguments are hypothesis-based and that there exist conflicting research results. Internet websites are effective media to send necessary information directly and continuously to the public.

2) Utilizing symposium

A symposium is a good opportunity for efficient information distribution, where the content of discussions can be designed flexibly so that effects can be maximized. For example, MOE needs to pay attention to the role of "program for general public" in MOE's international symposium. This program has been considered to be a supplement to "program for experts" which is the main part of international symposium. But hereafter, it is required to effectively utilize the "program for general public" to raise the level of understanding of ordinary citizens, where it is indispensable to provide easy-to-understand information. It is also necessary to verify proper understanding of attendants through checkup of their feedback.

As for the "program for experts," participation of experts from various countries is important, since international cooperation is essential to promote studies on endocrine disruptors. MOE's international symposium will continue to provide valuable international opportunities for information exchanges among experts. Also, MOE will continue to maintain bilateral cooperation, including the existing Japan-UK and Japan-the Republic of Korea joint programs, to further promote information exchanges.

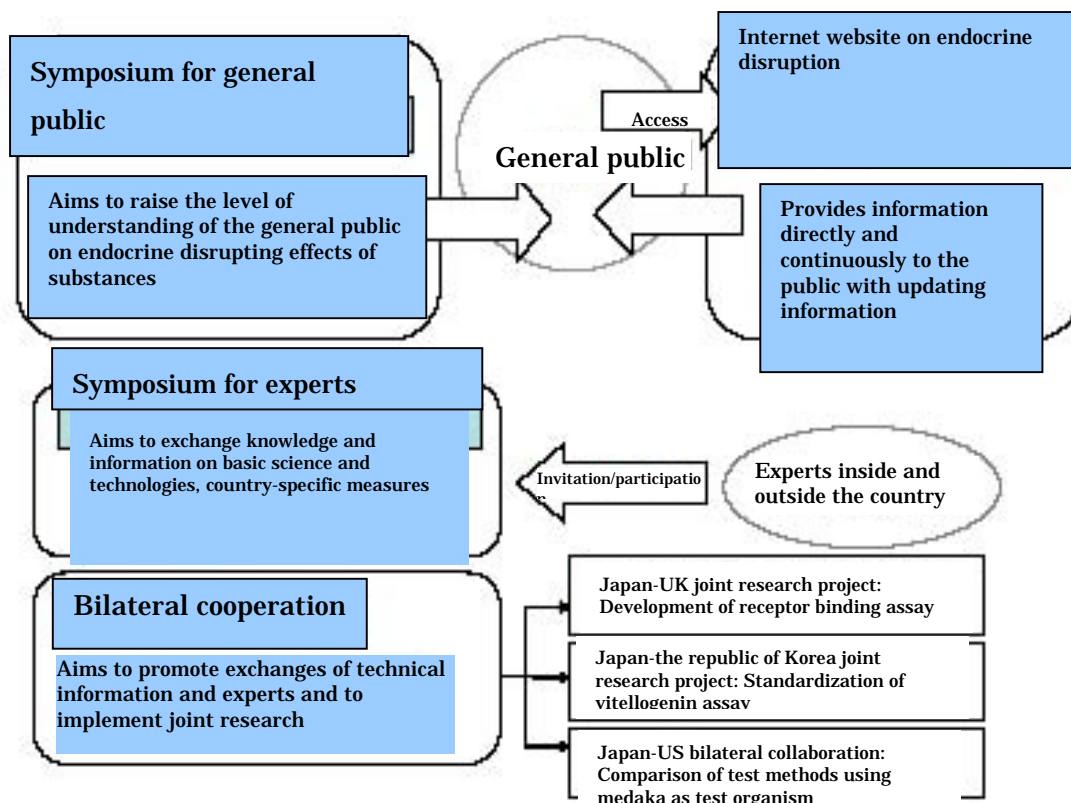


Figure 8 Conceptual diagram of Approach toward promotion of information sharing

3) Promotion of information sharing multilaterally by the ministries, industries, academia, local public organizations and the general public

It is important for relevant ministries and agencies of the government to promote information exchanges among them while clarifying their respective roles (Figure 9).

It is desired that not only the government but also experts, industries (chemical suppliers, etc.) and academic organizations will actively provide relevant information as necessary.

In addition, MOE intends to assist local public organizations in promoting community-level information sharing by providing them with all necessary information in a timely manner.

MOE also hopes to see active commitment by the general public for the promotion of information distribution, based on enriching scientific sound understanding on endocrine disruption.

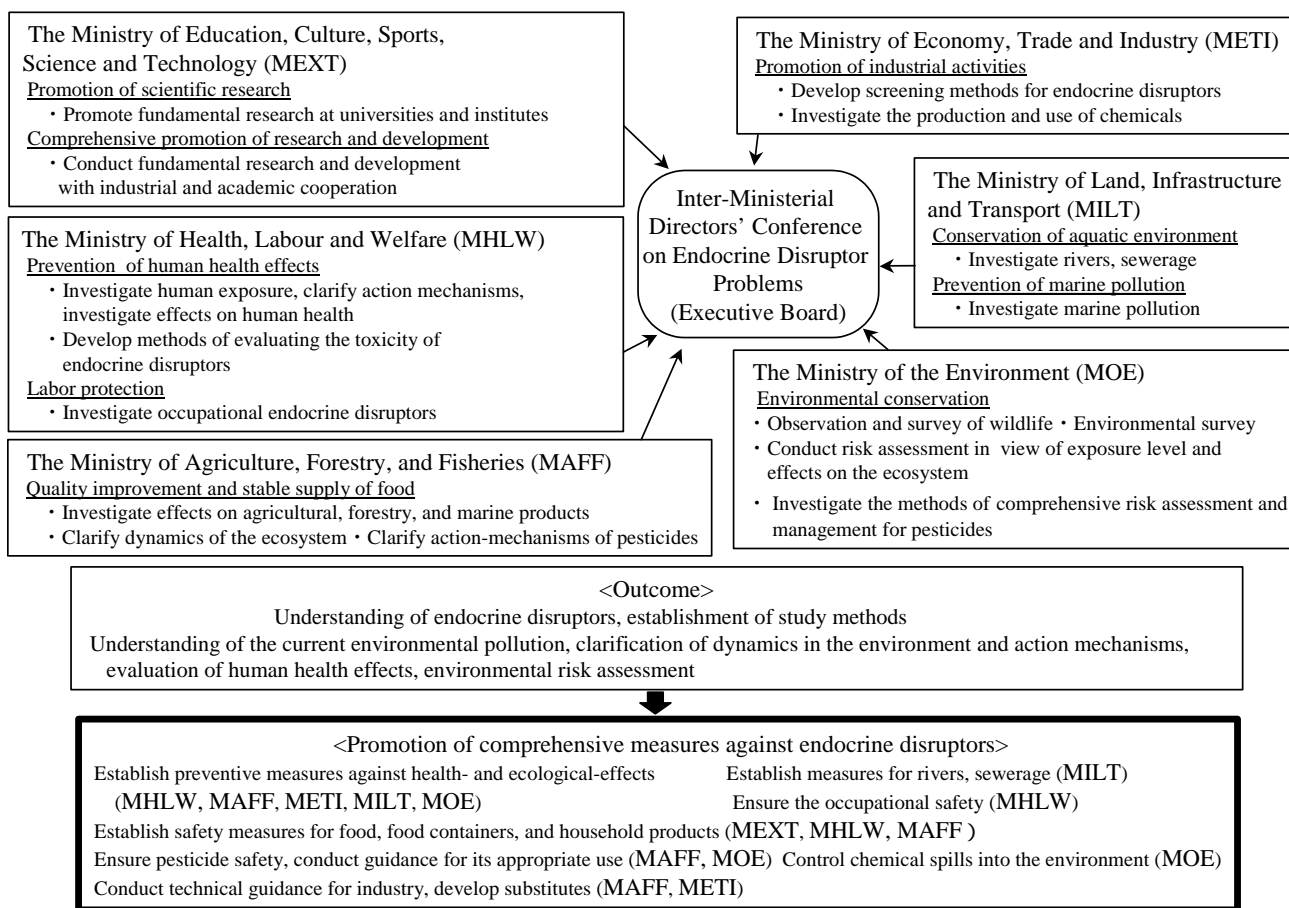


Figure 9: Inter-Ministerial Cooperation on Endocrine Disruptor Problems

Risk communication

According to the 2004 Environmental White Paper issued by MOE, risk communication in the field of chemicals can be defined as the efforts to promote mutual understanding and information sharing among all units of the society, including general public, industries and governments, on accurate knowledge regarding chemicals.

Generally, risk communication in the field of chemicals is based on bilateral information exchanges between a pollution-causing industry and general public of an affected community with the aim of finding effective measures to prevent pollutions and promote self-management of the industry. However, in the field of endocrine disruptors, where the level of social anxiety tends to be especially high due to the presence of various scientifically-unknown factors, multilateral information exchanges involving various people in different fields and positions are essential. First of all, it is necessary to find the most effective, practical way to develop risk communication on endocrine disruptors, where experts and specialists in this field are expected to play an important role.

At the same time, MOE considers it important to create information sharing opportunities involving the general public, experts, industries and governments (Figure 10), for the purpose of

promoting mutual understanding among them. One of the good examples of such opportunity is a round-table meeting among representatives of general public, industries and governments hosted by MOE for discussing the environmental risks of endocrine disruptors. (<http://www.env.go.jp/chemi/entaku/index.html>) It is hoped that such opportunities will be created by local public organizations also. Through interviews conducted by MOE over local public organizations to find their opinions and approaches (Appended Materials 6), it became evident that they were also aware of the importance of risk communication. Therefore it is hoped and expected that community-level risk communication will be further promoted and that such communication will effectively respond to local needs.

Sense of values varies according to individuals, and there are various kinds of opinions on how environmental risks of endocrine disruptors should be managed or how much risk can be considered as acceptable. In the light of such diversity of opinions, it is important to create opportunities to deepen mutual understanding.

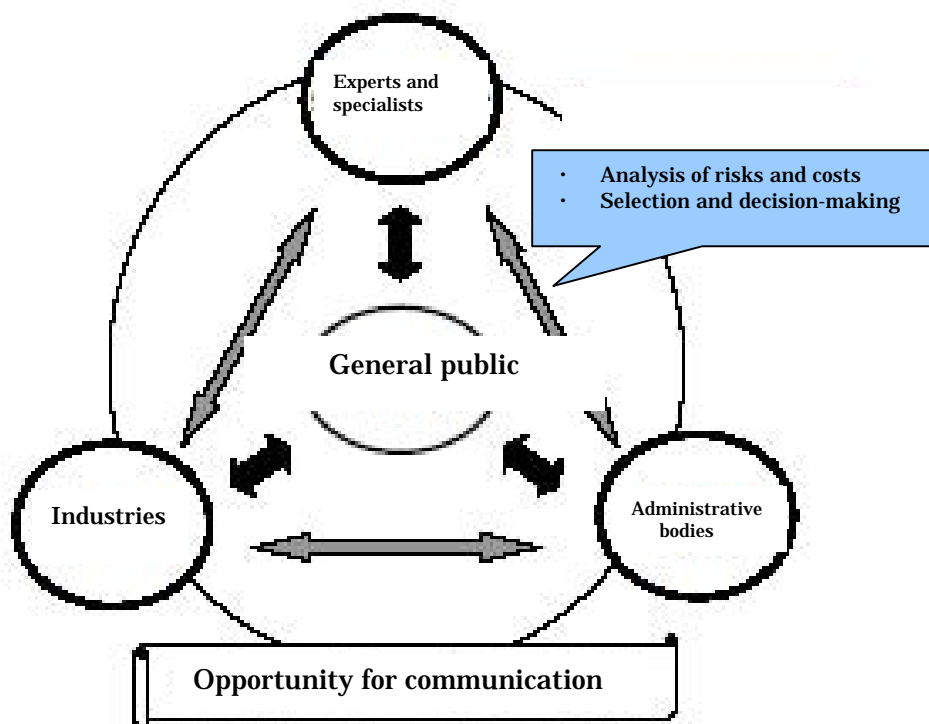


Figure 10: Concept of risk communication

Environmental education

There is an opinion that teaching scientific knowledge to children at the early age might be dangerous because of the possibility of creating biased opinions/attitudes due to the immature

ability of those children to accurately understand and critically assess science. Meanwhile, it is also true that children are already exposed to considerable amounts of scientific information. Information on endocrine disruptors is complicated and difficult to understand even for adults. Also, such information has been attracting a lot of public attention because of the alleged serious impacts on future generations. In addition, it is concerned that children could be influenced by opinions of adults close to them or affected by social anxiety without a clear understanding of the issue.

It is hoped that well-designed educational programs for children will be developed so that children can foster their ability to make appropriate, independent judgment, when they are grown up, on potential risks, benefits and costs of chemicals and make a decision at their own discretion on how to use chemicals. In an effort to help children foster such ability, MOE intends to promote distribution of easy-to-understand information designed for children. It is also hoped that the administrative bodies, industries and academic organizations should make efforts to release reliable information and at the same time offer effective educational tools to help children understand the information properly.

Conclusion

In order to implement effective measures in accordance with the policy and future plans mentioned herein, it is necessary to establish a comprehensive and open-to-the-public planning/evaluation scheme for all necessary surveys, researches and projects. See Figure 11 for the framework of overall approaches to address the issues of endocrine disruptors.

It is important that all information and research results obtained through implementation of administrative measures be shared with international communities. To this end, MOE needs to actively participate in international activities, such as standardization process of test methods. In addition, further efforts will be necessary to clarify roles of respective ministries and agencies and promote information exchanges among relevant organizations.

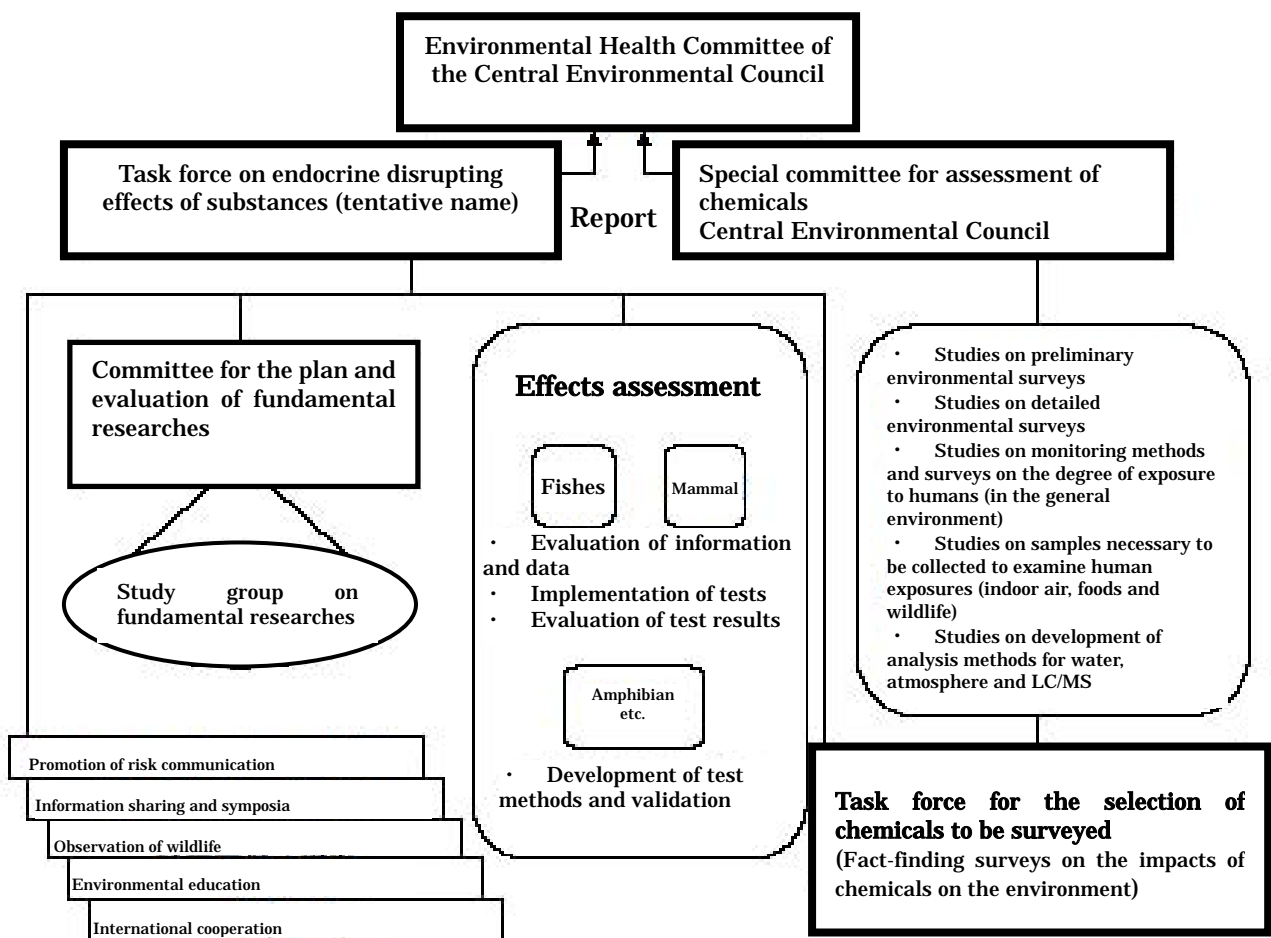


Figure 11: Comprehensive framework of measures to be implemented by MOE

MOE intends to promote effective measures aggressively in accordance with the policy and objectives mentioned in this document, with aiming to meet people's needs and contribute to international activities.

All objectives and planned measures mentioned above in this document are based on scientific knowledge and information MOE has obtained by the time of writing. It is expected that any

necessary revision to this report will be made whenever it is appropriate to do so, judging from any new scientific information, data or knowledge obtained through future researches and/or surveys.