RISK ASSESSMENT OF ENDOCRINE DISRUPTERS

1st MEETING OF THE VALIDATION MANAGEMENT GROUP FOR NON-ANIMAL TESTING (VMG NON-ANIMAL) OF THE TASK FORCE ON ENDOCRINE DISRUPTERS TESTING AND ASSESSMENT (EDTA)

There is still scientific uncertainty about the effects of endocrine disruption on human health and the ecosystem, as pointed out by many experts. Thus, it is important to identify the exact harmful effects induced by suspected endocrine disrupters by accumulating the results and data of scientific researches and assessments on the issue in cooperation with relevant authorities, so as to deal with the adverse effects (toxicity) on the basis of appropriate risk assessment.

1. Hazard/risk assessment of the chemical substances suspected to have endocrine disrupting effect

(1) Hazard assessment

For 15 groups of chemical substances* which are among “chemical substances suspected to have endocrine disrupting effects” (67 groups of substances) in the “Strategic Programs on Environmental Endocrine Disrupters, 1998 (SPEED ’98)” published by the Environment Agency of Japan, excluding those that have not been produced or used in Japan and other groups of chemicals to which various measures have been already taken (e.g. pesticides, dioxins), hazard assessment has been conducted to respond to social demand for the immediate scientific assessment of these substances. Hazard assessment reports have been compiled through examination of the adverse effects related to endocrine disruption as well as collection and evaluation of a wide range of data which is needed to assess their effects on human health.

* (1) octachlorostyrene (6) polybromobiphenyl (11) di-2-ethylhexyl adipate
   (2) styrene dimer/trimer (7) 2,4-dichlorophenol (12) di-n-butyl phthalate
   (3) n-butyl benzene (8) diethyl phthalate (13) di-2-ethylhexyl phthalate
   (4) dicyclohexyl phthalate (9) butyl benzyl phthalate (14) nonyl phenol
   (5) benzophenone (10) 4-nitrotoluene (15) bisphenol A

In the future, these reports will be updated on a regular basis, and additional examination of effects on the ecosystem will be conducted. Of the above 15 groups of chemical substances, intensive study of related literature on effects on the ecosystem is to be conducted for those
substances for which further assessment is considered necessary from the aspects of their production volume and level of possible exposure. When conducting the assessment, the outcome of the most recent studies regarding assessment of risk to the ecosystem is to be given due attention.

Further, the addition of other chemical substances to be subjected to hazard assessment will be considered as necessary, taking into account the screening data obtained based on the provisional testing and assessment scheme (now planned in METI, see 3. below), as well as relevant hazard/exposure information, etc.

(2) Risk assessment/management

Among the chemical substances suspected to have endocrine disrupting effects, for those substances for which the adverse effects have been pointed out, whether or not they have endocrine disrupting effects, with reference to the results of above-mentioned hazard assessment, it is essential to conduct exposure assessment through prediction of behavior in the environment on the basis of release survey and monitoring as well as risk assessment on human and ecosystem, and to examine appropriate measures for risk management.

The appropriate measures for risk management of chemical substances will be developed within the “Comprehensive Evaluation & Management Program for Chemical Substances” that was initiated in 2001, in which risk assessment of chemical substances subjected for PRTR has been conducted. The developed measures are to be incorporated into the endocrine disrupters testing and assessment scheme (see 3. below).

In FY 2002, the “Risk Assessment & Management Study Groups” for nonyl phenol, bisphenol A and some phthalic esters were established within the National Institute of Technology and Evaluation (NITE) by inviting experts from both academia and industry to be members. In these three Study Groups, deliberation on appropriate risk assessment measures is underway in coordination with the Comprehensive Program.

2. Establishment of the endpoints and development of relevant test methods

While studying out the validity of screening methods under development, the establishment of relevant testing methods is to be pursued.

(1) Screening methods

For the purpose of establishing screening methods to efficiently pick up the chemical substances that may have endocrine disrupting effects, development of a technique of three-dimensional quantitative structure activity relationship (3D-QSAR) is underway as a screening method using computers, aimed at producing a prototype within FY 2002. As in vitro screening
methods, reporter gene assays, receptor binding assays, thyroid hormone effects assay and receptor non-mediated endocrine disrupting effects assay are also being developed. Furthermore, while participating in the international validation study organized by the OECD, development of screening methods using mammals (uterotrophic assay, Hershberger assay and enhanced TG407 (28-day repeated dose toxicity study)) is underway.

(2) Definitive test method

For the purpose of appropriate assessment of the adverse effects (toxicity) caused by endocrine disrupters, establishment of the endpoints and definitive test methods to assess those endpoints is needed. To this end, research on a improved two-generation reproductive toxicity test method and an in utero lactation assay have already been started.

3. Development of endocrine disrupters testing and assessment scheme

It is essential to take advantage of the results of research and development so far obtained, to efficiently screen and categorize those chemical substances that may have endocrine disrupting effects from among a huge number of chemical substances, to conduct hazard assessment and exposure assessment, and to effectively define and assess the risk presented by these chemical substances.

In June 2002, the 6th meeting of the OECD Task Force on Endocrine Disrupters Testing and Assessment (EDTA 6) was held in Tokyo, and “OECD Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals” was established. In this framework, the assessment of each chemical substance should be based on a case by case basis, taking into account all available information, and bearing in mind the function of the framework levels. The member countries agreed to continue the discussion on testing and assessment strategies and the Conceptual Frameworks in the international cooperative manner.

In METI, with reference to the outcome of EDTA 6, a provisional testing and assessment scheme that focuses on the effects on human health is under development (see Figure). Screening of major chemical substances which are produced in or imported into Japan in an amount of 100 tons or more annually (estimated to be several thousand of chemicals) and/or which have been detected with certain volume in the environment through monitoring, etc. is to be started under this scheme from FY 2003. At the same time, the study on the scheme will be carried out for further improvement under international collaboration.
Figure  Provisional Endocrine Disrupters Testing and Assessment Scheme of Human Health Hazards

**Initial Sorting**
Production/Import volume, molecular weight, human exposure data, hazard data, use pattern, etc.

**Prescreening (Information on mechanisms)**
1) Sex hormone receptor recognition/binding (agonistic/antagonistic activity)
2) Arylhydrocarbon receptor (AhR) recognition/binding (agonistic activity)
3) Effects on aromatase activity
4) Thyroid hormone receptor recognition/binding (agonistic/antagonistic activity)
5) Chemical structure relating to thyroid hormone biosynthesis inhibitor
6) Others

**Screening (in vivo hormonal activity)**
- Uterotrophic assay
- Hershberger assay
- Enhanced repeated dose 28-day oral toxicity test

Evaluation of *in vivo* hormonal activity

**Definitive Testing (Reproductive and developmental toxicity, etc.)**
- Enhanced one-generation test (or in utero through lactational exposure test)
- Enhanced two-generation reproduction test

**Definitive Testing not needed**
**Definitive Testing needed**

**Risk management**

**Hazard assessment**
Exposure assessment

**Risk assessment**

**Other hazard information**

**Non-Assessed Chemicals (NAC)**

**Non-Target Chemicals (NTC)**

*The combination of *in vivo* tests will be flexibly made according to the results obtained by "Prescreening."*

**The combination of tests or experimental protocol for test has been determined yet**