

Hazard Assessment
of Some Chemical Substances Which Have Been
“Suspected to Be Endocrine Disrupters”

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Sub-Committee for Endocrine Disrupters
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Document of hazard assessment of individual substances of chemical materials which were pointed out as “being suspected of having endocrine-disrupting action”

As regards endocrine-disrupting substances (so-called environmental hormone-disrupter), scientific uncertainty is being pointed out internationally in many cases at present. In order to correctly grasp their impact on human health and ecosystem, it is necessary to conduct many scientific studies and evaluations. At the same time, as to adverse effects (toxicity) brought about by endocrine-disrupting action, it is necessary to take effective measures based on scientific findings.

Therefore, to sufficiently accumulate scientific findings necessary for assessment of risks, the Ministry of Economy, Trade and Industry (METI) set up Subcommittee on study of endocrine-disrupting action in the Department of examination and management, of the Council on chemical substances. The said subcommittee was set up in August 1999 as a subcommittee on study of endocrine-disrupting action in the Council on chemical substances (Chairman of the subcommittee: Junshi Miyamoto, who is former director of the department of chemistry and environment, International Union of Pure Applied Chemistry). With this subcommittee as working center, METI has been collecting various types of scientific information, and as to chemical substances which were “suspected of having endocrine-disrupting action”, efforts were made to develop testing methods necessary for assessing hazard of the chemical substances pointed out, and for sorting out and evaluation of such substances.

[Hazard assessment of individual substances]

- I. From the chemical substances which were listed in the then Environment Agency’s “SPEED ‘98, a strategic program against environmental hormone-disrupters” as “being suspected of having endocrine-disrupting action” (group of 67 substances ^(Note)) and as requiring investigation and study thereafter, the Subcommittee on study of endocrine-disrupting action removed groups of those which were not manufactured or used in our country, and those such as registered agricultural chemicals and dioxin, for which countermeasures were being taken, and for the

^(Note) In the “SPEED '98, a strategic program against environmental hormone-disrupters (Nov. 2000 edition)”, styrene dimer/trimer, and n-butyl benzene were deleted, leaving 65 items in the list.

remaining 15 items mentioned below, assessment of hazard was made, as urgent measures, so as to meet the social demand that scientific evaluation and verification be made as soon as possible.

- (1) Octachlorostyrene
- (2) Styrene dimer and trimer
- (3) n-Butylbenzene
- (4) Dichlorohexyl phthalate
- (5) Benzophenone
- (6) Polybrominated biphenyl
- (7) 2,4-Dichlorophenol
- (8) Diethyl phthalate
- (9) Butylbenzyl phthalate
- (10) 4-Nitrotoluene
- (11) Adipic acid di-2-ethylhexyl
- (12) Di-n-butyl phthalate
- (13) Di-2-ethylhexyl phthalate
- (14) Nonyl phenol
- (15) Bisphenol A

- II. In hazard assessment of individual substances, the endocrine-disrupting substances were defined as follows:

“Exogenous substances that bring about changes in endocrine system of individual living body, thereby inducing health damage to the individual living body or its offspring” (Opinion of EU/WHO/OECD workshop, December 1996). Thus, it was recognized as important to assess the health damage brought about as a result of disruption of the endocrine system. Consequently, in confirming hazard, importance was placed on their impact on human health.

Concrete methods of investigation are shown below:

Retrieval of information was conducted mainly by “TOXLINE” and “MEDLINE”, which are considered to cover nearly all information necessary for assessment of impact on human health. In addition, necessary information was retrieved and

collected by referring to literature cited in overseas assessment data (IARC monograph, EHC, BUA, NTP, BIBRA, ACGIH, etc. (Time of retrieval: Substances (1) - (9), April 2001; Substances (10) - (15), October 2000). Databases (HSDB, PHYSPROP, etc.) were also used in part. Data on physicochemical properties were quoted from HSDB and PHYSPROP, and as regards data on biodegradability, test results based on the guidelines of the Chemical Substances Assessment Law were shown. Acute toxicity values were quoted mainly from the above-mentioned overseas assessment data, and when necessary, original articles were examined in detail.

Also, when necessary, literature published after the above retrieval time and up to November 2001, and data etc. reviewed in NTP low dose peer review were collected.

Furthermore, test results not put into the form of formal articles were also adopted if they had been evidently reviewed by specialists and the testing facilities have been identified. As regards the results of related tests METI entrusted to the Chemical substances Evaluation Research Institute (CERI), those which received specialists' peer review were reflected in the assessment.

Those who kindly extended their cooperation in review of the results of CERI's related tests are shown below:

Hiroaki Aoyama	The Institute of Environmental Toxicology
Kiyoshi Imai	Food and Drug Safety Center, Hatano Research Institute
Katsushi Suzuki	Nippon Veterinary and Animal Science University
Michihito Takahashi	Showa University
Tsutomu Nishihara	Osaka University Graduate School
Masatoshi Matsuo	Osaka University

III. The results of the assessment were classified and organized for each substance according to the following items, and entire description of the results etc. of the hazard assessment was reviewed by specialists. These results were summarized into the Documents of hazard assessment of individual substances (draft) (Details are shown in the attached sheets). At the meeting of the Subcommittee on

endocrine-disrupting action, this Document of assessment was approved as a draft to be published for inviting opinions from within Japan and from other countries as well.

The items to be classified and organized in the Document of hazard assessment of each individual substance are as follows:

1. Toxicity Data
 - 1) Information on adverse effect on human health
 - 2) Information on endocrine system and reproductive system
 - (1) *In vitro* test results related to receptor binding
 - (2) *In vivo* test results in mammals
 - 3) Information on general toxicity
 - (1) Acute toxicity
 - (2) Repeated-dose toxicity
 - 4) Information on mutagenicity, genotoxicity, and carcinogenicity
 - (1) Mutagenicity and genotoxicity
 - (2) Carcinogenicity
 - 5) Information on immune system
 - 6) Fate and Metabolism
2. Hazard assessment at present
3. Risk assessment and other necessary future measures

The following specialists kindly extended their cooperation in review of the results etc. of hazard investigation.

Katsumi Imaida	Kagawa Medical University, Pathology I
Makoto Shibutani	National Institute of Health Science, Biological Safety Research Center, Division of Pathology
Tomoyuki Shirai	Nagoya City University Medical School, Pathology I
Michihito Takahashi	Showa University
Masae Tatematsu	Aichi Cancer Center, Hospital and Research Institute
Hiroyuki Tsuda	National Cancer Center, Research Institute, Experimental Pathology and Chemotherapy

Masahiro Tsutsumi	Nara Medical University Cancer Center, Oncological Pathology
Dai Nakae	Sasaki Institute, Pathology
Shoji Fukushima	Osaka City University Medical School, Pathology I
Keisuke Yamashita	Hiroshima University School of Medicine, Anatomy I

Concerning 15 substances, the accuracy and validity of descriptions were reviewed, the work being assigned to each.

< Members of the Subcommittee on study of endocrine-disrupting action >

Junshi Miyamoto	Senior Adviser on Problems of the Environment, International Union of Pure and Applied Chemistry
Taisen Iguchi	Bioenvironmental Research, Center for Integrative Bioscience, Okazaki National Research Institutes
Tohru Inoue	Biological Safety Research Center, National Institute of Health Sciences
Shinichiro Kawai	Kobe College, Human Sciences
Tomoyuki Shirai	Nagoya City University School, Pathology I
Hiroaki Shiraishi	National Institute for Environmental Studies, Environmental Chemistry Division
Shinkan Tokudome	Nagoya City University Medical School, Public Health
Kazuko Matsumoto	Waseda University
Keisuke Yamashita	Hiroshima University School of Medicine, Anatomy I

IV. The Document of hazard assessment of individual substances was summarized as shown above, and it is published now so as to invite opinions from within Japan and from other countries as well.

For some of these substances, related tests (screening test, and 2-generation reproductive toxicity test) are being conducted, and their results are to be reflected in this Document of assessment. When any new findings are obtained concerning hazard, assessment will be reviewed accordingly.

Further investigations of hazard will be made hereafter concerning impact of individual substances on ecosystem.

If, in addition to the group of 15 substances, there are any industrialized chemical substances for which scientific assessment and verification are considered necessary at an early date from the standpoint of endocrine-disrupting action, efforts will be made for collection of new scientific findings in an organized manner, and assessment of hazard will be started.

As regards a chemical substance, in which any hazard has been pointed out as a result of hazard assessment, risk assessment will be made as the next step, regardless of the presence or absence of endocrine-disrupting action, based on the results of hazard assessment and exposure assessment, and when necessary, study will be made as to how proper risk management should be.