Framework for Quantitative Ranking of Endocrine-Disrupting Chemicals According to Risk

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Abstract

Endocrine-disrupting chemicals (EDCs) issues in Japan indicate the importance of the need to develop tools that can assist decision makers and consumers in the management of chemicals according to risk, even without sufficient scientific knowledge for general risk assessment. Risk comparison and risk ranking can provide a practical alternative to the general risk assessment. Risk comparison should be performed hierarchically with more intellectual levels of analysis and more data needs from one tier to the next. In this paper, a framework for risk comparison of EDCs is presented. The relative risk of estrogen mimics was evaluated on the basis of the product of the EDC estrogenic potential and body burden or the product of the EDC estrogenic potential and blood level. The relative risks of controversial anthropogenic chemicals are comparatively smaller than that of estradiol or genistein.

1. Introduction

The introduction of "*Our Stolen Future*"(1) to the Japanese society and the release of a list of 67 chemicals, which are suspected to be EDCs by the Environment Agency, in 1997 aroused consumers' fears of adverse health effects from exposure to endocrine-disrupting chemicals (EDCs). Thus some plastic food containers which contain chemicals such as bisphenol A, phthalates and styrene dimers that might contaminate food, were even boycotted. Numerous municipalities decided to change the polycarbonate dishes used for school meals to those of other plastics or nonplastics at the parents' request, because such dishes might release bisphenol A. In 1998, the sales of instant food packaged in polystyrene containers dropped by 15% for fear of the release of styrene dimers from the container. Consumers' motivation lacks a scientific basis and is irrational in terms of how to reduce risks with limited resources. However, such consumers' behavior is understandable, because they are given no information about the

magnitude of risk from EDCs. In contrast, the message that EDCs might harm humans, as well as the suggestion that one should adhere to the precautionary principle of avoiding suspected chemicals, is repeatedly conveyed to them via mass media.

In this context, it is imperative to provide information to consumers and decision makers regarding the magnitude of risk from EDCs. Needless to say, it is impossible to carry out generic risk assessment of EDCs at present, because little scientific knowledge is available. Therefore, we must seek another substitute that can assist decision makers and consumers to make rational decisions in terms of risk management. It is not reasonable that one must wait for a complete general risk assessment without taking any measures against EDCs. For this purpose, the best strategy is to perform risk comparison or relative ranking of the risks of EDCs. Risk comparison should be performed hierarchically with more intellectual levels of analysis and increased data needs from one tier to the next. In Japan, considering consumers' fears, the human health risk should be evaluated first, although the assumed adverse effects of EDCs on ecological health are anticipated to be more intense than on human health.

The risk comparison should have the following characteristics.

1. Risks that are compared should be as similar as possible; in this context, the risk is relative.
2. Risk comparison should be carried out between EDCs sharing similar mechanisms.
3. Risk should be evaluated for the most sensitive receptors and the worst-case scenarios
4. Relative risks are evaluated by considering the endocrine-disrupting potential, exposure and bioavailability of EDCs.
5. Surrogate parameters are used for final parameters. In other words, surrogate endpoints are used for final endpoints. However, surrogate parameters are replaced by more reliable ones as more scientific knowledge becomes available.

In this regard, Safe has suggested that the dietary contribution of estrogenic industrial compounds is 0.0000025% of the average daily intake of estrogenic flavonoids in the diet, based on their consumption coupled with their estimated estrogenic potencies[(2)]. In addition, Calabrese et al. proposed a toxicologically based scheme for quantitative ranking chemical agents with respect to their capacity to cause endocrine disruption in target species such as humans, fish and birds, based on short-term bioassays[(3)]. In this paper, not only the estrogenic potential, but also the exposure and bioavailability of EDCs are considered.

2. Basic Framework

2.1 Endocrine-disrupting potential

In carrying out human health risk assessment of EDCs, the endpoint of the final assessment is not endocrine disruption itself, but other outcomes resulting from the endocrine-disrupting mechanism, such as carcinogenic, reproductive or developmental effects. Of these final endpoints, the major concern in this study is the effects on the development of reproductive capability. Therefore, emphasis is placed on EDCs that include estrogen receptor (ER) agonists which are called estrogen mimics, ER antagonists which are called estrogen inhibitors, and

androgen antagonists which are called androgen inhibitors. In the absence of epidemiologic studies, we must use short-term bioassay tests and test-animal toxicology studies to evaluate their endocrine-disrupting (ED) potential. Furthermore, currently, we must rely almost entirely on *in vitro* bioassay test studies since *in vivo* test studies, which are more important than *in vitro* test studies, are not always possible.

We must establish a hierarchy of test methods with credibility grades from lowest to highest, since we must use a variety of test methods depending on the circumstances. In Table 1, one example of a hierarchy of estrogenic activity tests which are thought to be applicable for the evaluation of the relative estrogenic potential of EDCs is shown.[(4)-(6)] The test methods with higher credibility are placed more to the right. It will be possible to use tests with higher credibility to evaluate the magnitude of adverse effects via the endocrine system, as more knowledge is accumulated.

Table 1. Hierarchy of Estrogenic Activity Bioassay Tests for Estrogen Mimics

Low ◀——— Credibility ———▶ High

	In vitro			*In vivo*		
	Receptor Binding Assay	Transcriptional Expression	E-Screen Assay	Uterotrophic Response (Uterus weight)	Vaginal cornification	Reproductive disability
Bisphenol A	+	+	+	+		NOAEL=50mg/kg/day for rat
Nonylphenol	+	+	+	+ NOAEL=30 mg/kg/day(rat)	+	NOAEL=10mg/kg/day (?) three generation test for rat
Phthalates, BBP	+	+	+	—		
o,p'-DDT	+	+	+		+	+ (op'- and pp'-)
Styrene dimer				—		

Characteristics about five chemicals listed are cited from Ref.[(6)]

The initial stage involves *in vitro* ER binding assays which may be used to determine the ability of a given compound to compete with radiolabeled 17 β -estradiol (E_2) in binding to ER. The binding ability of a chemical relative to E_2 is represented as the relative binding ability (RBA). This assay is rapid and inexpensive, although it does not distinguish between estrogen mimics and estrogen inhibitors. The next stage involves *in vitro* ER-transcription assays. Binding of estrogen to ER in target cells results in the initiation of specific transcriptional activation events. The relative receptor-dependent transcription activity (RTA) is given as the ratio of the ER-transcriptional activity of xenoestrogens to that of E_2. This assay can distinguish estrogen mimics and estrogen inhibitors and has relatively high sensitivity[(7)]. The third stage includes the E-Screen assay in which estrogen-induced increase in the number of human breast MCF-7 cells is measured, which is recognized to be biologically equivalent to the increase in mitotic activity in the rodent endometrium [(8)]. In this assay, the relative proliferative potency

(RPP) is given as the ratio between E_2 and xenoestrogen doses needed to produce maximum cell yields. The RPP is used in this study as a measure of relative estrogenic potential.

Table 2. Characteristics of selected EDCs

2-1 Estrogen mimics

Chemical	Abbr.	Another function & Notes	Estrogenic activity		
			RBA	RTA	RPP
17 β -estradiol	E_2	Natural hormone	1	1	1
Diethylstilbestrol	DES	Synthetic hormone	2.5[9]	0.6[14]	10[8]
Nonylphenol	NP		0.0001[9], 0.003[10], 0.0005[15], 0.0009[15] 0.00026[16]	0.003[9], 0.0002[14]	0.00003[8]
Octylphenol	OP		0.00045[9], 0.0006[10] 0.0002[15], 0.0007[15] 0.00072[16]	0.001[9]	0.0003[8]
Bisphenol A	BPA		0.00012,0.0003[9][10] 0.0001[15], 0.0001[16]	0.00007[14]	0.00001[12]
Phthalates	BBP		<0.0005[9]	0.000001[9]	0.000003[8]
	DBP		<0.000005[9]	<0.000001[9]	
	DEHP		not active	not active[9]	
	MEHP				
Styrene dimer					
Polychlorinated biphenyls(PCB)	TCBB		<0.0014[9]		
	4OH2'4'6'-TCB	Weak antiestrogen? Tyroid active?	0.024[15], 0.047[15]	0.01[9]	0.0001[8]
	4OH2'3'4'5'- PCB		0.034[15], 0.072[15]		0.00001[11]
	Other OH-PCB		0.001～0.05[15],		<0.00001[11]
Dieldrin			0.00002[9]	0.00003[9]	0.000001[8]
o,p'-DDT, DDE	o,p'-DDT,DDE	p,p'-DDT is Androgen inhibitor	0.004[9], 0.0001[15], 0.0002[15]	0.001[9] NM[14]	0.000001[8]
Toxaphen			0.00002[9]		
Endosulfan			0.00002[9], <0.0001[15]		0.000001[8]
Methoxychlor					0.000001[8]
Zearalenone	ZE	Weak antiestrogen	0.05[11]	0.01[9]	0.01[8]
Coumestrol			0.3[10], 0.1[11]	0.01[9, 14]	0.00001[8]
Genistein		Weak antiestrogen Phytoestrogen	0.3[11]	0.01[9], 0.000045[13]	0.00026[13]

RBA =Relative Binding Ability, RTA= Relative Transcriptional Activity, RPP=Relative Proliferative Activity (mainly by E-Screen), E-Screen= see text.
BBP=Butylbenzyl phthalate, DBP=Dibutyl phthalate, DEHP=Di(2-ethyl-hexyl)phthalate
MEHP=Methylhexyl phthalate, TCBB= 343'4'-Tetrachlorobiphenyl,
4OH2'4'6'TCB=2'4'6'-Trichloro-4-biphenylol, 4OH2'3'4'5'-PCB=2'3'4'5'-Tetrachloro-4-bisphenylol

2-2. Estrogen inhibitor(Antiestrogen)

Chemicals	Mechanism
Dioxin	Ah-receptor-dependent, 1TEQ=1EQ , Thyroid hormone receptor responsive
PCB	Ah-receptor-dependent, 1TEQ=1EQ , Thyroid hormone receptor responsive
Atrazine	not receptor- dependent
Indole-3-carbinol	

2-3. Androgen inhibitor

Chemicals	AR Binding Ability	AR-dependent transcriptional activity
Vinclozolin	+	+
p,p'-DDE	+	+

2-4. Others

Chemicals	Mechanism
1,2-Dibromo-3-chloropropane	not EDC?
Tributyltin	not EDC?

In Table 2, selected EDCs, which have been the cause of public concern because of their suspected endocrine-disrupting activity, are listed and classified into four categories: estrogen mimics, estrogen inhibitors, androgen inhibitors and others[(9)-(17)]. The RBA, RTA and RPP values are shown for the estrogen mimics.

2.2 Exposure Scenarios

Exposure analysis is the most important step in risk assessment. However, the exposure assessment component for risk comparison is qualitative or semiquantitative at best. In this case, it is necessary, first of all, to determine the most sensitive receptor and most important exposure pathway and postulate the worst-case exposure scenario. For the worst-case scenario, the risks of different EDCs are compared.

The US Environmental Protection Agency's special report has stated that "exposure to a single xenoestrogenic chemical, at current environmental concentrations, is probably insufficient to evoke an adverse effect in adults. More information is needed to determine whether this holds for the human fetus and the neonate." [(17)]. In other words, the most sensitive receptor is the human fetus and the neonate and the most important exposure pathway is that from the mother. Thus, the receptors to be examined in this study are identified as the fetus and neonate.

3. Results and Discussion

3.1 ED activity estimation based on EDC body burden

The relative risks of several of the estrogen mimics listed in Table 2 were calculated relative to that of E_2. Generally, the magnitude of adverse effects from a chemical is controlled by the exposure amount and its bioavailability. According to Giesy, three of the most important

characteristics for determining the bioavailability of ER ligands are lipid solubility, biological half-life and strength of protein binding [10]. Of the three, only the biological half-life is considered in this work, and in short, it is postulated that the magnitude of risk to the receptors targeted in this study due to exposure to EDC is controlled by the product of the maternal body burden and ED potential.

Assuming a one-compartment model, the EDC maternal body burden was calculated. In addition, the following was assumed: the receptor's mother was exposed to the same daily amount of EDC for 25 years, her body weight was 60 kg and half-life and daily intake of EDCs were as shown in Table 3[2][6][10][18][19]. The asterisk indicates the measured half-life value in humans; the remaining values were estimated from the measured half-life of the chemical in test animals. The half-life of BPA in humans was assumed to be 210 hours, on the basis of the estimation of 21 hours for the half-life of BPA in rat, which was calculated by the author using data from the experiment on the pharmacokinetics of BPA[6]. Furthermore, half-life was assumed to be 5 days for NP on the basis of the result that the half-life of OP in rat is 5 hours[9]. The result that the half-life of NP in humans is 2 to 3 hours was not used in this study, because there is no denying the possibility its value might be underestimated[20]. The results for the EDC body burden are shown in Table3.

Table 3. EDC Body Burden and Relative Estrogenic Activity

		E2	DES	BPA	NP	Isoflavonoids	Genistein
Assumptions	Daily Intake (mg/day)	6[18]	125[6]	0.006[6]	0.1	1020[2]	40[6]
	Half-life in human body(day)	*0.56[10]	*1[10]	8.75	5	0.5	*0.5[10]
	RPP(*in vitro*)	1	10	0.00001	0.00003	0.00026	0.00026
	RUW(*in vivo*)[19]	1	0.743[18]	0.00005[18]	0.00005[18]	0.0033	0.0033[6]
Results	Body burden (mg)	4.87	181	0.0761	0.725	739	29.0
	Relative Estrogenic Activity (*in vitro*)	1	372	1.6×10^{-7}	4.5×10^{-6}	0.039	1.5×10^{-3}
	Relative Estrogenic Activity (*in vivo*)	1	28	7.8×10^{-7}	7.8×10^{-6}	0.50	0.020

* Measured for humans

Next, relative estrogenic activity, given as the ratio of the product of the body burden and RPP of EDC to that for E_2, is shown in Table 3. In parallel to the RPP of *in vitro* assay, *in vivo* relative estrogenic potential obtained from uterine weight bioassay in intact juvenile rodents, RUW (relative uterotrophic activity in uterine weight bioassay), was also used. The results are shown also in Table 3. Thus the estimated estrogenic activities of EDCs are used as their relative risk values. Generally, outputs of relative risks contribute to the relative ranking but are value-neutral in terms of risk or safety. However, it will be possible to determine, according to the circumstances, how safe or how risky xenoestrogns are, by comparing the relative risk of xenoestrogens with that of phytoestrogens or with a value of 1 which indicates the estrogenic

activity of estradiol.

As shown in Table 3, the relative risks on the basis of the *in vitro* assay are DES>> estradiol >>> genistein >> NP >> BPA, while the relative risks on the basis of the *in vivo* assay are DES > estradiol > genistein >>>> BPA=NP. This shows that both relative risks exhibit almost identical behaviors.

Table 4 Endocrine Disrupting Activity

4-1 Estrogen mimics

EDCs	Blood level (g/mL)	RPP	Relative ED Activity	Notes
Natural hormones	10^{-12}～10^{-7}	1	10^{-12}～10^{-7}	USEPA[17]
PCBs	2.09×10^{-9}	*0.0001	(2×10^{-13})	measured in Japan,1985[21]
o,p'-DDT	(0.06～$3)\times10^{-9}$	0.000001	4×10^{-14}	measured in developed countries[9]
Dieldrin	**8.4×10^{-11}	0.000001	8×10^{-17}	measured in Japan[22]
Genistein	**7.4×10^{-8}	0.00026	2×10^{-11}	measured in Japan[9]

4-2 Estrogen inhibitors

EDCs	Blood level	Relative ED Potential	Relative ED Activity	Notes
Dioxins	1.1×10^{-13}	1 E_2 equivalent[2]	1.1×10^{-13}	(g of TEQ/mL), measured in Japan[23]
PCBs (coplanar)	3.9×10^{-14}	1 E_2 equivalent[2]	3.9×10^{-14}	(g of TEQ/mL), measured in Japan[23]
p,p'-DDE	**5.4×10^{-9}	?		(g/mL) [22]
p,p'-DDT	**4.3×10^{-10}	?		(g/mL) [22]
p,p'-DDT (DDE)	(1～$4)\times10^{-9}$	?		measured in developed countries[9]

* RPP (all homologues) =RPP (4OH2'4'6'-TCB)

** Estimated from chemical level in breast milk

3.2 ED activity estimation based on blood EDC level

Next, the measured blood EDC level, instead of its estimated body burden, was used to obtain a more realistic value of the relative ED activity of EDCs. Blood level, RPP and relative estrogenic activity of several estrogen mimics which include some persistent organic chemicals and genistein, are shown in Table 4-1 [9][17][21]-[23]. Some blood EDC levels were directly measured and others (marked with double asterisks) were estimated from measured breast milk EDC levels. It is needless to say that the estrogenic activity thus estimated must reflect more accurately the real value than the values obtained in 3.1. A further advantage of this approach is

the comparison of the relative risk of EDCs with the blood E_2 level. The EPA's special report states that hormones are transported in blood at low concentrations (ng or pg/ml) in the free state or attached to carrier proteins, and that a normal human female is able to regulate a 10^{-9}g/ml concentration of estradiol without difficulty[17]. Comparing with a blood E_2 level of 10^{-9}g/ml , the estrogenic activity of genistein is 50-fold less and that of op'-DDT is only 10,000-fold less. The estrogenic activity of dieldrin is negligible. The estrogenic activity of PCBs must be much less than the value shown in Table 4, which was calculated under the assumption that the RPP values of all homologues are identical to that of 4OH2'4'6'-TCB which exhibits the highest RPP value among all PCB homologues.

In Table 4-2, the blood level of some estrogen inhibitors are shown. The relative antiestrogenic potential of 1 TEQ (2,3,7,8-tetrachlorodibenzo-p-dioxin toxic equivalent) of dioxins or coplanar PCBs is assumed to be approximately identical to 1 E_2 equivalent [2]. Thus the antiestrogenic activity is given by the product of the blood level and antiestrogenic potential of dioxins and coplanar PCBs. Further examination of the antiestrogenic activity is needed.

3.3 Discussion

There is controversy over the dose-response relationship of EDCs. The procedure used in this work is identical that with the assumption that the dose-response relationship is linear and free of a no-effects threshold. For the moment, we need not consider popular controversy as to whether or not a threshold exists, or whether or not an irregular response is seen at low doses, since when data and information are limited, and when much uncertainty exists regarding the mechanism of endocrine-disruptive action, models or procedures are preferred so that they will be compatible with the limited information. If firm evidence that the dose-response relationship for a chemical is different from the assumed one is presented, modifications can be made on an individual chemical basis.

In this work, of the three major factors influencing the bioavailability of chemicals, the two other than biological half-life were not considered. Of those two, the strength of protein binding has raised much concern, because some researchers have suggested that xenoestrogens have higher bioavailability than E_2, due to a weaker protein binding ability. The bioavailability of xenoestrogen will not be higher than fifty times that estimated without considering protein binding, even though the above suggestion is plausible, considering that approximately 2% of E_2 is free in blood [10].

4. Conclusion

The framework for risk comparison or quantitative risk ranking of EDCs was presented. It was shown that the RPP, one of the *in vitro* bioassay parameters used to evaluate the estrogenic potential of xenoestrogens, is effective for risk comparison. The data and parameters used in this paper may include inappropriate ones due not only to a lack of sufficient knowledge about reaction mechanisms but also to insufficient efforts in gathering already published data. We must focus on gathering data and parameters for the time being. However, if the parameters are

replaced by the best ones available at the time, the results can be utilized for decision making regarding precautionary actions, the priority of further tests or product choice by consumers and impact evaluation, even though the scientific knowledge may still be insufficient.

While the regulation of each EDC should be implemented based on multigeneration reproductive tests, multigeneration tests are not used routinely to detect possible EDCs other than chemicals for limited uses. In this context, *in vitro* bioassay will also be used in the future. In addition, it is noteworthy that ECDs may act cumulatively and with endogeneous hormones. Therefore the measurement of the total ED activity due to ECDs will be required. The framework thus presented will also be useful for this purpose.

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