REVIEW ARTICLE

Necessity to establish new risk assessment and risk communication for human fetal exposure to multiple endocrine disruptors in Japan

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ABSTRACT Our recent study clearly shows that fetuses are exposed to multiple chemicals including endocrine disruptors in Japan. Although the embryo and fetus stages are the most sensitive period to chemicals in humans’ life cycle, the health effects of the chemicals such as endocrine disruptors to them are largely unknown. The conventional risk assessment method cannot assess the risk to fetuses precisely. Now we need a new risk assessment, in which the target is fetuses and not the adults, in addition to the conventional risk assessment. At the same time, we also need a new strategy to practically eliminate the risk for the future generations. To make the strategy effective, we suggest a new approach to reduce the risk and avoid the possible adverse health effects, using primary, secondary and tertiary preventions as they are used in public health. We also suggest a new concept of "pre-primary prevention" to reduce the risk for fetuses. Furthermore, to make this method even more practical, we suggest a new risk communication method. In this paper, we present a framework of risk avoidance of multiple chemical exposure to fetuses.

Key Words: fetal exposure, endocrine disruptors, human, multi-chemical contamination, risk assessment, pre-primary prevention, risk communication, Japan

INTRODUCTION

It has been recently clarified that there are many chemicals that disturb the functions of natural hormones in the human body and wild life (Colborn et al., 1996; Guillette and Guillette, 1996; Mori, 2001). They are referred to as endocrine disruptors. Endocrine disruptors include natural products, pharmaceuticals, industrial products and environmental pollutants (Colborn et al., 1996; Mori, 2001). Recent studies show that increasingly high levels of endocrine disruptors appear in the global environment (Tanabe et al., 1994; Iwata et al., 1995; Blais et al., 1998).

Many studies of wild shellfish, fish, alligators, birds, whales and polar bears have already clearly shown that disturbances of hormonal regulation by endocrine disruptors induced adverse effects on animals' reproductive, immune and nervous systems (Colborn et al., 1996; Iguichi et al., 2001). In addition, several etiological investigations have shown the possible adverse effects on human health including regional declines in sperm count (Carlson et al., 1992; Auger et al., 1995; Swan et al., 1997), increases in hypospadias (Matlai and Beral, 1985; Paulozzi et al., 1997) and male and female reproductive disorders (Herman-Giddens et al., 1997; McLachlan et al., 2001; Sasco, 2001). Exposure to endocrine disruptors is thought to be a possible cause in human health (Sharpe and Skakkebaek, 1993; Toppari et al., 1996; Safe, 2000; Mori, 2001). A historical tragedy by synthetic estrogen, diethylstilbestrol (DES) was reported thirty years ago. Maternal DES therapy induced cervical and vaginal cancers to their daughters 15 to 30 years after the exposure in utero (Herbst et al., 1971; Herbst et al., 1974; McLachlan et al., 2001).

Low level exposure to endocrine disruptors occurs throughout our lives from food, air, water, soil, household products and probably during gestation and lactation (Needam and Sexton, 2000). Risks associated with this low level but constant exposure are still largely unknown and highly controversial (vom Saal et al., 1997; Ashby, 2000). However, in animal experiments, potential endocrine disruptors show some adverse effects on the development and/or function of the re-
productive system and nervous system, particularly when the exposure occurs in fetal or neonatal individuals (Newbold et al., 1984; Colborn et al., 1996; Newbold, 2001; Shibayama et al., 2001; Williams et al., 2001). Therefore, disturbances of hormonal regulation during fetal or postnatal development have been thought to induce long-term adverse effects on human health. However, the adverse effects of endocrine disruptors on humans are difficult to detect because there is a long time lag between the exposure and the effects (Triendl, 2001).

At present, we do not have a suitable risk assessment method for human fetal exposure to endocrine disruptors (Needham and Sexton, 2000). We don't know which chemicals are risky and which chemicals are safe with the current exposure level to the fetus. Under the present situation, it is very difficult to assess the risk precisely and to avoid it for the next generation regarding endocrine disruptors (Eduljee, 2000; Mori et al., 2001). Naturally, the womb should be a clean environment, with no man-made chemicals, because it is basically the whole universe for the fetus (Colborn, 2000).

It seems that we are now living in the era to establish a new risk assessment method, which focuses and benefits fetuses, and decides the right direction of the strategy to make the method more useful. Here, we summarize our current studies on human fetal exposure to endocrine disruptors in Japan, and propose a framework of a new risk assessment and risk communication method to reduce the possible risks for the future generations to come.

HUMAN FETAL EXPOSURE ASSESSMENT OF ENDOCRINE DISRUPTORS IN JAPAN

Our group has investigated fetal exposure to endocrine disruptors in Japan by analyzing umbilical cords and cord blood (Japan Environment Agency, 1999; Japan Environment Agency 2001; Takada et al., 1998; Takada and Kumata, 2002; Mori, 2001). Human umbilical cords, a part of the fetal tissue, were collected from normal newborns. Our studies have been approved by the Congress of Medical Bioethics in Chiba University, Yamanashi Medical College and Kyoto University. We also obtained all the mothers' permission to analyze their babies' umbilical cords.

The results of our studies on the human fetal exposure assessment are as shown in Table I.

We detected dioxins (PCDDs + PCDFs + Co-PCBs), PCBs, p,p'-DDT, p,p'-DDE, hexachlorobenzene (HCB), hexachlorocyclohexane (HCH), chlordane, endosulfan, bisphenol-A, tributyltin (TBT), heavy metals (cadmium and lead), and phytosterogens (genistin and daidzein) in human umbilical cords or cord serum. By studying umbilical cord tissue and blood, we found that the fetuses were exposed to multiple chemicals.

Our studies clearly show that more than twenty chemicals transfer from the mothers to their fetuses through the placenta, and some fetuses are highly exposed to several of these chemicals (Mori, 2001; Mori et al., 2001). It is known that a human fetus is toxicologically much more sensitive to chemicals than an adult (Moore and Persaud, 1998; Needham and Sexton, 2000). Therefore, we need to really focus our attention on establishing a new risk assessment for human fetal multi-chemical contamination (Mori et al., 2001).

Although it is very important to assess the risk of the exposure to multiple chemicals precisely (Triendl, 2001), it is impossible to know the exact quantity of chemicals existing in each person's body. Furthermore, recent scientific findings show that each person has different susceptibility to chemicals (Guengerich, 1998; Shalat et al., 1998; Sharp and Barrett, 2000). In the current exposure assessment, it is common to analyze the exposure level of each chemical in the body or organ at a specific time period (Zacharewski, 1998; Needham and Sexton 2000). Also, the current method of risk assessment is to assess the risk of each chemical using an animal test or epidemiological survey (Zacharewski, 1998; Ashby, 2000; Eduljee, 2000; Sasco, 2001), and the target of the current risk assessment is adults, not children or fetuses (Needham and Sexton, 2000). However, in reality, the fetuses who are more sensitive to chemicals are contaminated by many chemicals in Japan and not by one single chemical (Mori, 2001; Mori et al., 2001).

It has become clear that it is very difficult to assess the precise risk for fetuses who are exposed to multiple chemicals by the current exposure assessment and the risk evaluation method using animal experiments or an epidemiological survey (Zacharewski, 1998; Triendl, 2001).

Therefore, we are determined to establish a new evaluation method of health risk assessment of fetal exposure to several endocrine disruptors very urgently, in addition to the current risk assessment.

NECESSITY OF RISK COMMUNICATION

"Risk" means the probability of adverse effects that may occur (Tohyama, 1998). The current risk assessment has been influenced by the concept of the risk assessment that was established in 1983 by the U.S. National Research Council (NRC) (NRC, 1983; Eduljee, 2000). The NRC pointed out that the risk assessment should contain some or all of the following four steps.

1. Hazard identification: The determination of whether a particular chemical is or is not causally linked to particular health effects.
2. Dose-response assessment: The determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
3. Exposure assessment: The determination of the extent of human exposure before or after application of regulatory
Table 1  Chemicals, heavy metals and phytoestrogens in umbilical cords/cord serum in Japan

<table>
<thead>
<tr>
<th>chemical</th>
<th>No. of samples*</th>
<th>No. of samples contained chemicals**(%)</th>
<th>Mean ± S.D.</th>
<th>Median</th>
<th>Max.</th>
<th>Min.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected Eds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dioxins(pg-TEQ/g wet)</td>
<td>20</td>
<td>20(100)</td>
<td>0.031 ± 0.010</td>
<td>0.027</td>
<td>0.053</td>
<td>0.012</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>Total WHO-TEQ² (PCDDs + PCDFs + Co-PCBs)</td>
<td>11</td>
<td>11(100)</td>
<td>0.107 ± 0.040</td>
<td>0.110</td>
<td>0.170</td>
<td>0.042</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>PCBs(ng/g wet)</td>
<td>20</td>
<td>17(85)</td>
<td>0.006 ± 0.002</td>
<td>0.005</td>
<td>0.010</td>
<td>0.003</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>p,p'-DDT(ng/g wet)</td>
<td>20</td>
<td>20(100)</td>
<td>0.225 ± 0.121</td>
<td>0.225</td>
<td>0.440</td>
<td>0.064</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>p,p'-DDE(ng/g wet)</td>
<td>20</td>
<td>9(45)</td>
<td>0.038 ± 0.055</td>
<td>0.021</td>
<td>0.180</td>
<td>0.005</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>HCB(ng/g wet)</td>
<td>20</td>
<td>20(100)</td>
<td>0.023 ± 0.013</td>
<td>0.020</td>
<td>0.055</td>
<td>0.006</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>HCH(ng/g wet)</td>
<td>20</td>
<td>20(100)</td>
<td>0.015 ± 0.018</td>
<td>0.008</td>
<td>0.073</td>
<td>0.005</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>cis-chlorden(ng/g wet)</td>
<td>20</td>
<td>15(75)</td>
<td>0.013 ± 0.006</td>
<td>0.013</td>
<td>0.030</td>
<td>0.004</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>trans-chlorden(ng/g wet)</td>
<td>20</td>
<td>16(80)</td>
<td>0.031 ± 0.014</td>
<td>0.030</td>
<td>0.066</td>
<td>0.009</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>trans-nonachlor(ng/g wet)</td>
<td>20</td>
<td>20(100)</td>
<td>0.035 ± 0.019</td>
<td>0.032</td>
<td>0.073</td>
<td>0.007</td>
<td>Environment Agency, 2001</td>
</tr>
<tr>
<td>Endosulfan(ng/g wet)</td>
<td>20</td>
<td>18(90)</td>
<td>4.425 ± 5.037</td>
<td>1.940</td>
<td>15.240</td>
<td>0.350</td>
<td>Takada et al., 1998, Takada &amp; Kumata, 2002</td>
</tr>
<tr>
<td>Bisphenol-A(ng/g wet)</td>
<td>20</td>
<td>11(55)</td>
<td>1.280 ± 0.369</td>
<td>1.300</td>
<td>1.800</td>
<td>0.500</td>
<td>Muraoka et al., 2002</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium(ng/g wet)</td>
<td>11</td>
<td>5(45)</td>
<td>0.336 ± 0.720</td>
<td>0.300</td>
<td>0.460</td>
<td>0.290</td>
<td>Environment Agency, 1999</td>
</tr>
<tr>
<td>Lead(ng/g wet)</td>
<td>11</td>
<td>11(100)</td>
<td>27.102 ± 24.375</td>
<td>16.400</td>
<td>93.500</td>
<td>7.920</td>
<td>Environment Agency, 1999</td>
</tr>
<tr>
<td>Phytoestrogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daidzein(ng/ml)</td>
<td>10</td>
<td>9(90)</td>
<td>4.678 ± 2.730</td>
<td>3.600</td>
<td>10.000</td>
<td>1.700</td>
<td>Environment Agency, 2001</td>
</tr>
</tbody>
</table>

%: Incidence(***/)
Eds = Endocrine Disruptors
WHO-TEF: Toxicity Equivalent Factor (WHO, 1998)
TEQ² (Environment Agency, 2001)
HCB = Hexachlorobenzene
HCH = Hexachlorocyclohexane
TBT = Tributyltin
controls.

4. Risk characterization: The description of the nature and often the magnitude of human risk, including attendant uncertainty.

The US Environment Protection Agency (EPA) is also trying to establish a risk assessment paradigm in the "Framework for planning endocrine disruptor research" (Kavlock et al., 1996; Reiter, 2001). With that, the first step is called Hazard Identification, the second step is the Dose-Response Assessment and Exposure Assessment, and the third step is called Risk Characterization. In any approach, hazard identification is required before the risk assessment. However, it is quite difficult to identify the hazard of chemicals in many cases. In the White Paper published by EU, the "Strategy for a Future Chemicals Policy" (2001) is mentioned with the following quote, "The lack of knowledge about the properties, uses, exposure, and health and environmental impacts of chemical substances across the world, particularly for the so-called 'existing substances', is a major cause of concern. There are potentially 100,000 such chemicals produced and used in the EU that existed before new assessment procedures came into force in 1981 for 'new' substances marketed after that date. Sufficient information is available for a very limited number of existing substances on the risks they pose to human health and the environment." (EU, 2001).

In EU, the "burden of proof" will be shifted from authorities to industry under a clear set of legal obligations with a goal of ensuring a high level of protection of human health and the environment, by making industry responsible for the safety of its products.

We insist that the current risk assessment has several shortcomings. That is, 1) it assesses the risk of each chemical, but it doesn't assume the risk of multiple chemical exposure, 2) it sacrifices a tremendous number of test animals' lives, 3) it requires a large amount of financial cost, 4) the target of risk assessment is adults, and it doesn't focus on the risks to children or fetal development, 5) it can register the effect of a high dose of chemicals, but it cannot register the effect of long-term, low level exposure to multiple chemicals.

In the year 2001, the United Nations Commission on Human Rights concluded in its annual meeting on 27th of April, "Living in a pollution-free world is a basic human right". It was the first decision that the Commission addressed the links between environmental contamination and human rights (UN Commission on Human Rights, 2001). It seems that we are now living in the era where we need to rethink our relationship with chemicals.

Now, to protect the future generations, we suggest establishing a framework of a new strategy for risk avoidance, using approaches of public health. Fig. 1 shows the framework. First of all, to know the level of fetal contamination, the exposure assessment is necessary. Next, the risk assessment should be followed, but as we mentioned already, it is extremely difficult to assess the chemicals' risk precisely.

Almost everyone agrees that chemicals have both risks and benefits. There are two kinds of risks, which are 1) clear and high and 2) unclear or low. When the risk seems to be clear and high, such as dioxins and PCBs, the administrations and the industries take action to reduce the use or emission of them into the environment. Also, to reduce the risk, preventive medicine as it is used in public health can be applied in this problem. The preventive medicine contains primary prevention, secondary prevention and tertiary prevention. The primary prevention in risk avoidance is health promoting activities, such as not to intake chemicals which have adverse health effect. The secondary prevention consists of counseling for the high risk group to reduce the accumulated chemicals in the body, or again not to intake chemicals which have adverse health effect. The "high risk group" here means babies, their parents, young people who have genetically predictable adverse health effects after chemical exposure, and young women who accumulate a comparatively high level of chemicals in their bodies. The tertiary prevention consists of medical care for the group who shows the symptoms of potential adverse effects from endocrine disruptors such as the hypospadias, cryptorchidism, hyperactivity and hormone dependent cancers, so that they do not become worse.

On the other hand, after the risk assessment, if the risk is supposed to be unclear or low, such as endocrine disruptors or multiple chemical contamination, the administrations or the industries cannot or do not take actions. In the process of the current risk assessment and risk management method, there are always uncertainties on the estimation of the risk to children (Needham and Sexton, 2000). We propose here a new method to prevent the future risk, that is called Pre-primary prevention.

Pre-primary prevention is a new approach to avoid the risk of multiple chemical exposure to fetuses. In pre-primary prevention, there should be the promotion to reduce the chemical use in total or to reduce the amount of fetal exposure to chemicals even if the risk of each chemical is not clear.

To make the above steps possible, we need to establish a new method to reduce the risk for future generations by appealing to the society. We can do this through risk communication. Risk communication, which we are trying to establish here, especially focuses on the future generation and the fetuses. The current risk communication is defined by the Japan Environment Agency as, "All stakeholders such as administrations, industries, citizens, NGOs that have the precise information regarding environmental risk by chemicals, and they communicate it to each other." (Japan Environment Agency, 1998). However, this definition does not focus on the unique but adverse health effect to the fetuses by chemicals. Regarding the fetal exposure to multiple chemicals, pre-primary prevention may be the only way to reduce the future risk, and to make the pre-primary prevention effective, risk communica-
Strategic Framework for Risk Avoidance of Chemicals

**Fig. 1** Framework of risk avoidance of chemicals

The diagram shows the stream from the fetal exposure to the multiple chemical assessment, risk communication and risk management. Chemicals have both risks and benefits. When the risk is thought to be clear and high, the administrations and the industries can manage the risk. Also, preventive medicine (primary, secondary and tertiary preventions) can be applied to reduce the future risk. When the risk is thought to be unclear or low, the administrations and the industries cannot take action. Therefore, pre-primary prevention (preventive environmental medicine) and risk communication are useful and powerful strategies for risk avoidance.

**CONCLUSION**

It has become clear that human fetuses have been contaminated by multiple chemicals in Japan, and under the current situation, there are uncertainties regarding the risks to them (Needham and Sexton, 2000). We need to establish a new evaluation method for risk assessment of fetal exposure to endocrine disruptors, in addition to the current risk assessment method. At the same time, we need to reduce the exposure to multiple chemicals to fetuses. To do so, we suggest establishing a framework of risk avoidance of fetal exposure to multiple chemicals, using pre-primary prevention and risk communication. Pre-primary prevention means trying to reduce the chemical use in total or reduce the amount of exposure.
sure level to fetuses, even if the risk of each chemical is not clear. For this, environmental education will be effective.

The risk communication can be the most effective strategy to reduce the risk for human fetuses even if the multiple chemical exposure risk is not clear, and with that, public health and preventive medicine can be applied. Also, regarding fetal exposure, follow-up counseling will be necessary for the babies' parents and young women.

In the EU and the US, new suggestions to convert the idea of the risk have been published already (EU, 2001; O'Fallon et al., 2000; Needham and Sexton, 2000). It seems that the new method of risk avoidance, focusing on the fetuses, is longed by the society now.

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