Risk Assessment Studies
Report No. 48

Endocrine Disrupting Chemicals in Food

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EXECUTIVE SUMMARY

The Centre for Food Safety (CFS) has conducted a literature review on the endocrine disrupting chemicals (EDCs) in food and discussed the health risk associated with dietary exposure to these chemicals.

2. EDCs are naturally occurring or man-made substances that may mimic or interfere with the function of hormones, particularly the estrogens, androgens and thyroid hormones in the body. EDCs may turn on, shut off, or modify signals that hormones carry and thus affect the normal functions of tissues and organs. In recent years, there are growing concerns among scientists and the public at large on the potential adverse effects that may result from exposure to EDCs. International and national authorities are in the process of screening potential EDCs for setting research and management priorities.

3. The potential EDCs discussed by this study are high priority industrial chemicals considered by international and national authorities. They include organochlorine pesticides, dioxins and dioxin-like polychlorinated biphenyls (PCBs), bisphenol A (BPA), styrene, phthalates, organotins and nonylphenol (NP). These chemicals may have greater impact to the environment and human health compared to other potential EDCs because they are either persistent in the environment or high in production volume globally. To identify relevant literature, multiple database searches were conducted using internet search engines. All search terms were limited to publication dates ranging from 2002 to 2012 (inclusive) and with English or Chinese versions available. In addition, references were also made to relevant publications from international and national authorities.

4. Organochlorine pesticides are effective against a variety of insects but have been gradually phased out in recent years. Dioxins are ubiquitous in the environment, occurring naturally and as by-products of combustion and various industrial processes. PCBs were manufactured in the past for a variety of industrial uses but have been banned by most countries since 1970s. BPA and styrene are raw materials for manufacturing plastics and resins which are widely used in food packaging. Phthalates are a group of chemicals used as plasticisers, which improve flexibility and durability of plastics such as polyvinyl chloride (PVC). Organotins have been used extensively as biocides in wood preservatives, in antifouling paints for boats and as pesticides. NP is a building block of nonylphenol ethoxylates (NPEs), which are nonionic surfactants and can reduce surface tension of liquids such as cleaning agents. NP is also a raw material for producing additives of plastics (e.g. PVC) and rubber. The potential endocrine effects of these chemicals on reproduction, development and neurobehavioural development in humans are of particular interest to scientists.

5. Overseas data on organochlorine pesticides (including dichlorodiphenyl trichloroethane (DDT), hexachlorobenzene (HCB) and mirex), dioxins and dioxin-like PCBs, BPA, styrene, phthalates, organotins and NP and local risk assessment studies on DDT and dioxins and dioxin-like PCBs showed that the dietary exposure of the general population to these chemicals was below their representative health-based guidance values (e.g. tolerable daily intake (TDI)). Overseas studies found that high consumption of seafood especially (bivalves) that were heavily contaminated with organotins and misuse of certain polyvinyl chloride (PVC) cling films that release excessive NP while contact with fatty foods could lead to exposure to these chemicals

occasionally exceeding the TDIs. Nevertheless, transient excursion above the TDI would be unlikely to cause health consequences provided that the average intake does not continuously exceed the TDI which emphasises on a lifetime exposure.

6. For potential endocrine disrupting effects in human, some epidemiological studies indicated that EDCs may be assoicated with various human health effects such as effects on reproduction, neural function, immune function and different types of cancers. However, international and national authorities commented that more data on EDCs are needed for drawing conclusions.

7. The above mentioned potential EDCs may present in food as contaminants from environment and food contact materials (e.g. food packaging, containers and tableware). Food is considered as an important source of exposure to these chemicals. To ensure food safety, CFS will keep in view the latest international risk assessments and management options on potential EDCs in food for follow-up actions.

8. To reduce dietary exposure to these chemicals, food traders should ensure that food on sale in Hong Kong complies with relevant regulations and is fit for human consumption. Manufacturers and suppliers of food contact materials should adopt good manufacturing practices and make sure that their products comply with recognised standards, i.e., standards stipulated by the European Commission (EC), the U.S. Food and Drug Administration (FDA), and the Ministry of Health (MOH) of the People's Republic of China. The public should maintain a balanced and varied diet so as to attain a good health and avoid excessive exposure to contaminants from a small range of food items, such as seafood, especially bivalves, as they generally

contain higher level of environmental contaminants such as some EDCs and metallic contaminants. The public should also buy food and food contact materials (including food packaging, containers and tableware) from reliable suppliers. When using plastic food contact materials, always follow manufacturer's instructions and pay attention to the suitability of the product for holding hot, fatty or acidic foods, or for use in microwave oven, etc. Misuse of these products may cause the migration of potential EDCs from the plastic materials to food.

Risk Assessment Studies –

Endocrine Disrupting Chemicals in Food

OBJECTIVES

This study aims to discuss potential endocrine disrupting chemicals (EDCs) in food and the health risk associated with dietary exposure to these chemicals by a literature review.

BACKGROUND

2. EDCs, also known as endocrine disrupters/disruptors, are naturally occurring or man-made substances that may mimic or interfere with the function of hormones, particularly the estrogens, androgens and thyroid hormones in the body. EDCs may turn on, shut off, or modify signals that hormones carry and thus affect the normal functions of tissues and organs. According to the definition given by the World Health Organization (WHO)/International Programme for Chemical Safety (IPCS) in 2002, an endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.[1] People are exposed to EDCs in their everyday lives because these chemicals are used in thousands of products and present in food as contaminants.

3. The endocrine system is a complex network of glands, hormones and receptors. The principal function of endocrine system is to provide the key communication and control link between the nervous system and bodily functions such as reproduction, immunity, metabolism and behaviour. Endocrine glands are situated at various sites around the body, and in specialised areas of the brain. The cells in these glands secrete specific chemicals called hormones. Hormones circulate

around the body via the blood stream. They modulate cellular or organ functions by binding with receptors in the target cells. Receptors in the target cells, once activated by binding of the hormone, regulate the functions and processes in the tissue through interactions with the cell's DNA or other complex intracellular signalling processes.[2]

4. Current knowledge on the exact mechanisms of action of EDCs is limited. Nevertheless, research showed that EDCs can act at multiple sites through multiple mechanisms of action. They may (i) mimic the biological activity of a hormone by binding to a cellular receptor, leading to an unwarranted response by initiating the cell's normal response to the naturally occurring hormone at the wrong time or to an excessive extent (agonistic effect); (ii) bind to the receptor but not activate it. Instead the presence of the chemical on the receptor will prevent binding of the natural hormone (antagonistic effect); (iii) bind to transport proteins in the blood, thus altering the amounts of natural hormones that are present in the circulation; and/or (iv) interfere with the metabolic processes in the body, affecting the synthesis or breakdown rates of the natural hormones.[2] EDCs may interfere with fundamental sex steroid effects on the brain, the pituitary gland, the gonads and the accessory sex organs, such as the uterus and mammary gland in females and the prostate and seminal vesicles in males.[3]

5. Some epidemiological studies indicated that EDCs may be assoicated with various human health effects such as effects on reproduction, endometriosis, precocious puberty, neural function (particularly prenatal exposure), immune function, different types of cancer (i.e. breast, endometrial, testicular, prostate and thyroid). However, further studies are needed to confirm the causal links.[1]

6. EDCs are not a defined group of substances. Potential EDCs include natural chemicals produced by plants (the so-called phytoestrogens) and certain fungi; synthetically produced pharmaceuticals like the contraceptive pills are intended to be highly hormonally active; and some man-made chemicals and by-products. These include some pesticides (e.g. DDT and other chlorinated compounds), chemicals in some consumer and medical products (e.g. some plastic additives), and a number of industrial chemicals (e.g. polychlorinated biphenyls (PCBs), dioxins). The hormonal activity of these chemicals such as nonylphenol (NP), a breakdown product of alkylphenol ethoxylate surfactants, is many times weaker than the body's own naturally present hormones.[2]

International Perspective

7. In recent years, there are growing scientific and public concerns on the potential adverse effects that may result from exposure to EDCs, in particular, the low-dose effects (namely those that may be relevant to actual human exposure levels) and the potential synergetic effect resulted from exposure to different EDCs. WHO/IPCS in 2002 assessed the association between EDCs and human health effects such as effects on reproduction, endometriosis, precocious puberty, neural function, immune function, and different types of cancer. WHO/IPCS opined that exposure to EDCs has been suggested to play a role in adverse health outcomes in human although information such as dose-response relationships and exposure data are lacking. Furthermore, the changes in human health trends in some areas for some outcomes are also sufficient to warrant concern.[1]

8. Identifying EDCs is the first step for reducing potential risks associated

with these chemicals. There are no authoritative lists of EDCs or potential EDCs. International and national authorities have taken initiatives to identify EDCs and study the associated risks to human and the environment. The WHO, IPCS, the European Commission (EC), and the U.S. Environmental Protection Department (USEPA) have agreed to exchange information and co-ordinate international research. The Organisation for Economic Co-operation and Development (OECD), the EC and USEPA are working on the development and validating of tests and test strategies that will be recognised and accepted by different international and national organisations.[2] Some OECD member countries such as Canada and Australia are also working on the global harmonisation of assessment methods designed to reducing endocrine-disrupting products.[4,5]

9. The EC Directorate-General for the Environment (DG Environment) has developed a priority list to prioritise further detailed review of potential EDCs. Chemicals in concern are classified into three categories: "Category 1" chemicals are those that have evidence of endocrine disrupting activity in at least one species using intact animals; "Category 2" chemicals are those that have at least some *in vitro* evidence of biological activity related to endocrine disruption; and "Category 3" chemicals are those that have no evidence of endocrine disrupting activity or no data available. At present, 66 out of 553 substances in the candidate list are assigned as "Category 1". They are mainly organochlorine pesticides and other industrial chemicals (including byproducts) such as dioxins and dioxin like-PCBs, bisphenol A (BPA) and styrene, phthalates, organotins, and alkylphenols including NP. They are either high production volume (HPV) chemicals or persistent chemicals. The DG Environment of the European Union (EU) stated that the list of chemicals is subject to change with the latest scientific knowledge.[6] The Ministry of the Environment,

Government of Japan also made a list of 67 suspected EDCs under its Strategic Programs on Environmental Endocrine Disruptors '98 (SPEED '98). Many chemcials in the list are the same as those listed in the EC's Category 1.[7] The lists of "Category 1" chemicals of the DG Environment and the 67 suspected EDCs by the Ministry of the Environment, Government of Japan are shown in Table 1 and Table 2 of Annex I.

10. In the U.S., the USEPA also has a screening program for potential endocrine disruptors. The screening method of the USEPA is different from that of the DG Environment. In the U.S., chemicals were selected based on the exposure potential but not the evidence of their endocrine disrupting effects. A total of 67 chemicals were included in the Final List of Chemicals for Initial Tier 1 Screening in 2009. These include pesticide active ingredients and HPV chemicals used as pesticide inert ingredients. A second list of chemicals for Tier 1 screening was developed in 2010. This list of 134 chemicals includes a large number of pesticides, two perfluorocarbon compounds (PFCs), and some pharmaceuticals. Due to the nature of the screening method, USEPA emphasised that the list was for screening propose only. So, it should not be construed or characterised as a list of known or likely endocrine disrupters.[8] The first and second lists of chemicals for initial tier 1 screening of USEPA are showed in Table 3 and 4 of Annex I.

11. A common international approach to the control of EDCs is to reduce their release into the environment and thus reduce their associated risk pose to humans and wildlives. Over the past few decades, many toxic chemcials that also have shown suspected endocrine disrupting effects were being either restricted or banned. Examples of these include the global phase out of DDT, chlordane and some other

persistent pesticides since the 1970s, the drastic decrease in the use of organic tin compounds such as triphenyltin(TPT) and tributyltin (TBT) as antifouling paints on ships in 1990, and the banning of the manufacture of baby bottles with BPA in many countries in recent years.[9,10,11]

12. WHO/IPCS in 2002 commented that environmental and tissue levels of certain chlorinated persistent organic pollutants (POPs) (e.g., PCBs) have declined in some countries in response to regulations banning or phasing out these chemicals, but they remain of concern in many countries and uncertainty still exists regarding future trends.[1] In fact, a study showed that temporal trends of levels of certain organochlorine pesticides (i.e. chlordane, DDT and hexachlorobenzene (HCB)) in sediment core of Deep Bay, an important water body between Hong Kong and Mainland China, generally increased from 1948 to 2004. The authors commented that historical mass-production and ongoing production and usage of some organochlorine pesticides and intermediates in China may partly explain the trends.[12] For chemicals other than POPs such as BPA and NP, a study showed that levels of these chemicals were increasing since 1990s in the sediment of Pearl River Estuary and the adjacent South China Sea because of constant economic growth and lack of adequate wastewater facilities.[13] The environmental levels of potential EDCs of concern greatly depend on many factors such as the persistency of the chemicals as well as the environmental policies, production volumes and uses of the chemicals in different countries.

13. As for regulatary control of EDCs in food, there is not a set of international or national standards established specifically for EDCs or potential EDCs. Nevertheless, a wide range of chemicals are regarded as potential EDCs. Codex and

food safety authorities in different countries have set regulatory standards for some of them under various standards such as contaminants, pesticide and veterinary drug residues, and food contact materials (e.g. food packaging, containers and tableware).

Local Situation

14. Similarly, there is no specific subsidiary legislation to govern EDCs or potential EDCs in food in Hong Kong although the CFS operates a food surveillance programme and regularly take food samples for testing of chemical hazards in which some of them are potential EDCs such as dioxins, some phthalates and pesticides. The Public Health and Municipal Services Ordinance (Cap. 132) stipulates all food on sale must be wholesome, unadulterated and fit for human consumption. The CFS takes a risk-based approach in controlling food safety. Endocrine disruption is one of the toxic effects of potential health hazards that are considered in risk assessment. To protect public health, appropriate risk assessment will be conducted if any potential health hazard in food is identified.

15. The adverse health effect on humans due to dietary exposure to potential EDCs is uncertain and a topic of considerable research. Relevant information on these chemicals is needed for risk management and communication. Therefore, CFS conducted a literature review on EDCs in food as part of its risk assessment.

SCOPE OF STUDY

16. There is at present not an authoritive list of EDCs available and the potential EDCs are numerous. However, according to the screening lists of environmental authorities of the EC, Japan and the U.S., the potential EDCs of concern are mainly man-made chemicals which are either high in production volume

or persistent environmental contaminants.[6,7,8] They include organochlorine pesticides as well as industrial chemicals including dioxins and dioxin-like PCBs, BPA and styrene, phthalates, organotins, and NP. Food is an important source of exposure to these chemicals. This study focused on the above mentioned chemicals and reviewed current information on their toxicity and potential risks posed by these chemicals associated with dietary exposure. A summary of literature search strategy and sources of information are showed in Annex II.

POTENTIAL ENDOCRINE DISRUPTING CHEMICALS

I. Organochlorine Pesticides

17. Organochlorine pesticides are chlorinated hydrocarbons. The organochlorine pesticides with potential endocrine disrupting effects selected for discussion in this paper are chlordane, DDT, hexachlorobenzene (HCB), mirex and chlordecone, and toxaphane. They have been listed as the POPs under the Stockholm Convention due to their high persistence, tendency to accumulate in fatty tissues of living organisms and magnify along the food chain.[14] Therefore, they are of higher concern.

Uses

18. Organochlorine pesticides are effective in against a variety of insects. They were widely used since their introduction in 1940s but have been gradually phased out in recent years because of their environmental persistence and potential adverse effects on wildlife and human health.[15,16] However, under the Stockholm Convention, DDT can be used in disease vectors control in accordance with WHO recommendations and guidelines.[14]

Sources of exposure

19. In the general population, diet is the main source of exposure to organochlorine pesticides, primarily through the ingestion of fatty foods such as dairy products and fish. Contaminated drinking water and air are usually minor exposure sources. Infants can be exposed through breast milk, and the fetus can be exposed in utero via the placenta. Workers can be exposed to organochlorines in the manufacture, formulation, or application of these chemicals.[15]

Toxicity

Chlordane

20. WHO classified chlordane as "moderately hazardous" for acute toxicity. Liver is the target organ for toxicity in mice. Chlordane has also been shown to affect the reproduction of experimental animals. Available evidence cannot conclude the genotoxicity of chlordane.[17] The International Agency for Research on Cancer (IARC) in 2001 classified chlordane as Group 2B, i.e. possibly carcinogenic to humans.[18] The Joint Food Agriculture Organization (FAO)/WHO Meeting on Pesticide Residues (JMPR) established an acceptable daily intake (ADI) of 0.0005 mg/kg body weight (bw)/day for chlordane in 1986.[17]

Dichlorodiphenyl trichloroethane (DDT)

21. WHO classified DDT as "moderately hazardous" for acute toxicity.[19] DDT was also reported to cause liver damage in experimental animals and impair reproduction and/or development in a number of animal species. In addition, some breakdown products of DDT can cause harmful effects on the adrenal gland.[20] DDT is not genotoxic. IARC in 1991 classified DDT and associated compounds as Group 2B, i.e. possibly carcinogenic to humans.[21] JMPR established a provisional tolerable

daily intake (PTDI) of 0.01 mg/kg bw for DDT and its associated compounds in 2000.[20]

Hexachlorobenzene (HCB)

22. WHO classified HCB as "extremely hazardous" for acute toxicity.[19] HCB has been shown to cause death, systemic (e.g. liver, skin, bone, and thyroid), neurological, developmental, endocrine, and immunological toxicity in humans. Animal studies have demonstrated that HCB causes reproductive toxicity and increases the risk for cancer formation. The most sensitive target organs for hexachlorobenzene are the liver, ovary and central nervous system.[22] HCB has not been found to be genotoxic in most studies conducted to date. IARC in 2001 classified HCB and associated compounds as Group 2B, i.e. possibly carcinogenic to humans.[21] The USEPA established a reference dose for chronic oral exposure (RfD) of 0.0008 mg/kg bw/day for HCB in 1991.[23]

Chlordecone

23. The acute oral toxicity of chlordecone for experimental animal is moderate. Animal studies showed chlordecone is toxic to liver as well as thyroid, kidney and nervous system.[24] Chlordecone is not genotoxic. IARC in 1987 classified chlordecone as Group 2B, i.e. possibly carcinogenic to humans.[25] USEPA established an RfD of 0.0003 mg/kg bw/day for chlordecone in 2009.[26]

Mirex

24. Mirex has similar structure as chlordecone. The acute oral toxicity of mirex for experimental animal is moderate. Animal studies showed mirex is toxic to liver as well as thyroid, kidney and nervous system.[24] Mirex is not genotoxic.

IARC in 1987 classified mirex as Group 2B, i.e. possibly carcinogenic to humans.[25] USEPA established an RfD of 0.0002 mg/kg bw/day for Mirex in 1992.[27]

Toxaphene

25. Toxaphene is highly toxic following acute oral exposure by experimental animals. Animal studies showed toxaphene is a developmental toxicant and toxic to nervous system.[28] Toxaphene is not genotoxic. IARC in 2001 classified toxaphene and associated compounds as Group 2B, i.e. possibly carcinogenic to humans.[18] JMPR and USEPA have not established any safety reference dose for chronic exposure to toxaphene. The Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. derived a minimal risk level (MRL) of 0.002 mg/kg bw/day for intermediate-duration oral exposure (15– 364 days) to toxaphene.[28]

Endocrine disrupting effects

26. WHO/IPCS commented that from a neurobiological point of view, disruption of organisational factors during brain development is important because long lasting or irreversible neurobehavioral changes later in life may be the consequence of such interactions. For example, thyroid hormones are known to affect brain development by increasing the rate of neuronal migration to specific brain areas.[1]

27. Some organochlorine pesticides have been found to have effects on thyroid in humans. Those that have received the most attention are persistent pesticides such as DDT and HCB.[29] Both DDT and HCB were found to produce anti-thyroid effects in pregnant women.[30, 31] Organochlorine pesticide exposure is associated with neurodevelopmental health effects in humans. Studies showed in utero exposure to organochlorine pesticides was linked to decreased psychomotor function and mental

function, including memory, attention and verbal skills in children.[32,33] Maternal residence near agricultural areas where organochlorine pesticides were applied has been associated with lower performance on numerous neurobehavioral assessments in children.[34]

28. Many organochlorine pesticides are *in vitro* estrogen receptor agonists. The associations between cancers and exposure to these chemicals have been studied extensively. The assessment of the DG Environment concluded that results of studies of breast and prostate were inconclusive but there was good evidence that organochlorine pesticides act as androgen receptor antagonist. Diminished androgen action in fetal life are linked to risk factors for testicular germ cell tumors. However, the associations between organochlorine pesticides and testicular germ cell tumors found in epidemiological studies were relatively weak.[29]

Levels in food and dietary exposure estimation

29. Food commodities may contain traces of persistent organochlorine pesticide residues due to environmental pollution even though they are no longer be used as pesticides at present. The USFDA has analysed a number of organochlorine pesticides including chlordane, DDT, HCB and Mirex in food in its Total Diet Study (TDS). Results showed that the levels the above mentioned organochlorine pesticides were below limit of quantification in nearly all food commodities tested. Those with detectable levels contain only traces of organochlorine pesticides.[35] The CFS has conducted a risk assessment study on dietary exposure to DDT of secondary school students in Hong Kong in 2006. It was found most food samples contained non-detectable amount of DDT. The dietary exposures to DDT for average and high consumers were 0.145 and 0.291 μg/kg bw/day respectively. Both levels fell well

below the PTDI of 0.01 mg (10 μg)/kg bw/day established by JMPR. It could be concluded that both the average and high consumers of the secondary school students were unlikely to experience major toxicological effects of DDT.[36]

Standards/regulatory limits of pesticides in food

30. For the above mentioned organochlorine pesticides, Codex has set maximum residue limits (MRLs) for chlordane and DDT in specified food commodities.[37] In addition, the EU has set MRLs for chlordecone.[38] Most of these MRLs are in fact the detection limits of the pesticides.

31. Regarding the regulation of pesticide residues in food in Hong Kong, the Public Health and Municipal Services Ordinance (Cap.132) stipulates that all food on sale must be wholesome, unadulterated and fit for human consumption. To further safeguard public health, the Government has introduced the Pesticide Residues in Food Regulation under the Public Health and Municipal Services Ordinance. This Regulation will come into operation on 1 August 2014 after a grace period of some 2 years.[39]

II. Dioxins and Dioxin-like Polychlorinated Biphenyls (PCBs)

32. Dioxins are a group of polychlorinated, planar aromatic compounds with similar structures, chemical and physical properties. Distinct by its chemical structure, dioxins can be grouped into polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), whereas "dioxin-like PCBs" refers to polychlorinated biphenyls (PCBs) that exhibit toxicological properties similar to dioxins. Due to similarity in toxicity profiles and mechanisms of action, dioxins and dioxin-like PCBs are generally considered together as a group although their sources

are different.[40,41] Dioxins and dioxin-like PCBs persist in the environment and bioaccumulate in the food chain. Dioxins and dioxin-like PCBs are POPs under the Stockholm Convention.[14]

Uses

33. Dioxins are ubiquitous in the environment, occurring naturally (e.g. volcanic eruptions and forest fires), and as by-products of combustion (e.g. waste incineration) and various industrial processes (e.g. production of chemicals, chlorine bleaching of paper pulp and smelting). In contrast, PCBs were manufactured in the past for a variety of industrial uses such as electrical insulators or dielectric fluids and specialised hydraulic fluids, and their uses have been banned by most countries since 1970s. However, their release into the environment still occurs from the disposal of large scale electrical equipment and waste.[40,42]

Sources of exposure

34. Persons can be exposed to PCDDs, PCDFs and coplanar PCBs occupationally, accidentally, or in the environment (background). Exposure to background contamination can occur by inhalation, ingestion, or contact with contaminated soil. The exposure assessment by the European Food Safety Authority (EFSA) showed that > 90% of the exposure of a typical person to PCDDs, PCDFs and coplanar PCBs came from food and predominantly from animal fat.[40]

Toxicity

35. The acute toxicity of different dioxin congeners varies widely between and among species, e.g. the oral median lethal doses were 0.6 and > 5000µg/kg bw in guinea pigs and hamsters respectively. However, acute toxicity data on individual dioxin-like PCB congeners in mammals were limited. For long-term environmental

exposure, a range of toxic effects may be caused, including immunotoxicity, developmental and neurodevelopmental effects, and effects on thyroid and steroid hormones and reproductive function. Fetus or neonate is considered as the most sensitive life stage.[43]

36. Regarding the carcinogenicity of dioxins and dioxin-like PCBs, experimental animal and epidemiological studies in occupational settings indicate carcinogenicity at multiple sites in a range of animal species and human. IARC classified 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PeCDF) and 3,3',4,4',5-pentachlorobiphenyl (PCB-126) as Group 1 agents, i.e., carcinogenic to humans; five other PCDDs and ten PCDFs as Group 3 agents, i.e., not classifiable as to their carcinogenicity to humans; and other PCBs as Group 2A, i.e., probably carcinogenic to humans.[43, 44, 45, 46] Available information showed dioxins and dioxin-like PCBs are not genotoxic. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable monthly intake (PTMI) of 70 pg/kg bw/ month for PCDDs, PCDFs and dioxin-like PCBs expressed as toxic equivalent (TEQ).[43]

Endocrine disrupting effects

37. Two incidences of contamination of cooking oil in Taiwan and Japan and epidemiological studies in the U.S. showed exposure to PCBs, among other contaminants, adversely affected the neurobehavioural development of children such as lowering their IQ.[29] WHO/IPCS opined that neonatal PCB exposure had been reported to have a negative impact on neurobehavioural development which caused delay in postnatal psychomotor, neurological or cognitive development. However,

whether the development delay persists was considered controversial, and the mechanistic basis for these effects was unclear.[1]

38. Some studies showed exposure to dioxins influences male reproductive system. Exposure to TCDD during infancy and puberty leads to permanent reduction of estradiol and increased follicle-stimulating hormone in men. These effects are permanent and occur at TCDD concentrations < 68 ppt, which is within one order of magnitude of those in the industrialised world in the 1970s and 1980s and may be responsible at least in part for the reported decrease in sperm quality, especially in younger men.[47] The DG Environment stated that associations between testicular germ cell tumors risk and exposure to PCBs have been detected in several epidemiological studies, but the magnitude of effects is relatively small. Very likely only a fraction of the real existing risks has been captured. There was a strong exposure-response relationship for PCBs and prostate cancer mortality among the U.S. workers engaged in capacitor manufacturing.[29]

Levels in food and dietary exposure estimation

39. Dioxins can be concentrated in the food chain so that livestock, fish, and shellfish can have higher concentrations than the plants, water, soil, or sediments around them. The highest concentration of dioxins in livestock, fish, and shellfish, are typically found in fat and the liver.[48] CFS released the report on the First Hong Kong TDS on dioxins and dioxin-like PCBs in 2011. The dietary exposures to dioxins and dioxin-like PCBs were 21.92 and 59.65 pg TEQ/ kg bw/month for average and high consumer of the population, respectively, which amounted to 31.3% and 85.2% of PTMI.[49]

Standards/regulatory limits of dioxins and dioxin-like PCBs in food

40. The establishment of Codex guideline levels for dioxins in foods is under consideration. Meanwhile, WHO, in collaboration with the FAO, through the joint FAO/WHO Codex Alimentarius Commission, has established a "Code of Practice for the Prevention and Reduction of Dioxins and Dioxin-like PCB Contamination in Foods and Feed". This document gives guidance to national and regional authorities on preventive measures.[50]

41. In Hong Kong, there is no specific subsidiary legislation to regulate dioxins in food. Starting from 1999, the Government has been monitoring dioxins in foods as part of the food surveillance program. When dioxins are found to exceed the action level, risk assessment will be conducted to assess the associated health risk. An action level of 1 pg WHO-TEQ/g sample on product basis of PCDDs and PCDFs has been adopted in the routine food surveillance programme. A single action level is used for all food commodities.

III. Bisphenol A (BPA)

42. BPA is also known by its proper chemical name, 2,2-bis(4-hydroxyphenyl) propane.[51]

Uses

43. BPA a high-production-volume industrial chemical that is widely used in the production of polycarbonate (PC) and epoxy resins which are used as a protective lining in metal-based food and beverage cans.[51]

Sources of exposure

44. BPA may migrate from food packaging, such as plastic containers (including baby bottles) and coated food cans, into the food. Food is a major source of human exposure to BPA. Other less important sources of BPA are house dust, soil or toys, dental treatments and thermal papers (e.g. cash register receipts).[52]

Toxicity

45. BPA has low acute toxicity. There are no indications of any genotoxic or carcinogenic effects. The major concerns on BPA are its low-dose effects on reproductive system and neurobehaviour during the developmental period in experimental animals. The EFSA re-established a tolerable daily intake (TDI) of 0.05 mg/kg bw for BPA. This TDI was reconfirmed by EFSA in 2010.[51]

Endocrine disrupting effects

46. Some recent epidemiological studies have suggested associations of BPA exposure and adverse health effects (i.e. increase incidence of diabetes, reduced semen quality, caused male sexual dysfunction in adults and behavioural changes (aggression and hyperactivity) in young girls). Some of these studies have shortcomings in the design such as the use of data from self-reported diagnosis of pre-existing chronic diseases and incomplete assessment of occupational co-exposure of other chemicals. The EFSA and the Joint FAO/WHO Expert Meeting in 2010 both commented that it was difficult to draw any conclusions from these studies.[51,52]

Levels in food and dietary exposure estimation

47. Studies conducted in Canada, New Zealand, and the U.S. found most canned food tested contain BPA.[53,54,55] However, the BPA levels reported were well below the specific migration level (SML) of 0.6 mg/kg set by the EC. The Joint FAO/WHO Expert Meeting in 2010 estimated the international exposure to BPA. It considered a variety of possible scenarios of model diets, combining consumption from the worst-case scenario (100% of consumption from packaged food) to the best-case scenario (25% of consumption from packaged food) with concentration data reported from selected literatures. Consequently, a number of exposure estimates were derived.[52] The international estimates of exposure of all age groups by the Joint FAO/WHO Expert Meeting were well below the TDI of 0.05 mg/kg bw/day established by EFSA. This indicated health risk of all age groups due to current exposure of BPA is unlikely.

Standards/regulatory limits of BPA in food and food contact materials

48. There is no Codex and local standard of BPA in food. The EU and Mainland China have set a SML of 0.6 mg/kg for BPA from food contact materials into foodstuff.[56,57] BPA containing baby bottles were banned in many countries such as Mainland China, Canada and the EU.[9,10,11]

IV. Styrene

49. Styrene is produced in industrial quantities from benzene and ethylene. It is a colourless, viscous liquid with a pungent odour and tendency to polymerise. It is slightly soluble in water but very soluble in benzene and petroleum ether.[58]

Uses

50. The uses of styrene include intermediate in the manufacture of plastics, elastomers and resins which in turn are used in packaging foods, food products and various other processes in the food industry. It is also used as a synthetic flavouring substance and adjuvant.[59]

Sources of exposure

51. High level of styrene exposure mainly occurs in industries and operations using styrene by workers. The potential sources of general population exposure include motor vehicle exhaust, tobacco smoke, and other combustion/pyrolysis processes. Low level exposure of the general population can occur through the ingestion of food products packaged in polystyrene (PS) containers.[58]

Toxicity

52. Styrene is of low acute toxicity after inhalation or ingestion. Chronic exposure to styrene in human may have depressive effects on the central nervous system and is an irritant to epithelial surfaces. Human studies are inconclusive on the reproductive and developmental effects of styrene. An increased rate of spontaneous abortions was reported in a study of styrene workers, however, another study of occupationally exposed women failed to establish a link between the incidence of spontaneous abortions and styrene exposure. There are studies that suggest there may be an association between styrene exposure and hepatic dysfunction as well as an increased risk of leukemia and lymphoma. However, the evidence is inconclusive.[60] IARC classified styrene as Group 2B, i.e. possibly carcinogenic to humans.[61] JEFCA established a provisional maximum tolerable daily intake (PMTDI) of 0.04 mg/kg bw for styrene. Its presence in food should be

kept to its minimum as technologically achievable.[62]

Endocrine disrupting effects

53. Epidemiological studies showed occupational exposure to high doses of styrene resulted in endocrine disruption such as altered levels of thyroid hormones.[63] However, studies on endocrine disrupting effects in humans from dietary exposure to styrene are not available. An *in vitro* study conducted by a cup noodle company examined the effects of styrene monomer (SM), styrene dimers (SD) and styrene trimers (ST) on the estrogen receptor (ER) binding assay, the androgen receptor (AR) binding assay, the proliferation of MCF-7 human breast cancer cells, the steroidogenesis in Leydig cells of rats and the uterotrophic assay of immature rats. It found that SM, SD and ST did not significantly bind to ER or AR of rats, did not induce the proliferation of MCF-7 cells, did not inhibit testosterone production in Leydig cells of rats, and did not induce estrogen-like alteration in the uterus and vagina of immature female rats. Therefore, it appears that these SM, SD and ST have no endocrine-disrupting effects through ER, AR and steroidogenesis mechanisms.[64] The Ministry of Health and Welfare of Japan stated that SM, SD and ST have neither proliferation potency against MCF-7 cells nor ER-binding capacity but chemicals suspected of being endocrine disruptors may express their actions through mechanism. For example, tributyltin (TBT), a kind of organotins, expresses its action by enzyme inhibition and dioxin expresses its action by binding to other receptors. Therefore, possible endocrine-disrupting actions like these of styrene cannot be ruled out.[63]

Levels in food and dietary exposure estimation

54. Styrene has been detected as a natural constituent of a variety of foods and

beverages, the highest levels occurring in cinnamon. PS and its copolymers are widely used as food packaging materials. The ability of styrene monomer to migrate from PS packaging to food has been reported in a number of publications and probably accounts for the greatest contamination of food by styrene monomer. A study of 12 commodities collected from the U.S. market showed the concentrations of styrene in cinnamon ranged from 1 690 to 39 200 ng/g, in beef samples ranged from 5.25 to 7.85 ng/g and in coffee beans from 1.57 to 7.85 ng/kg. Wheat, pecans, oats strawberries, and peaches showed no styrene concentrations greater than 3 ng/g. No detectable styrene was found in tomatoes, milk, or chicken.[65]

55. A study used food consumption data of Irish children aged 5-12 and migration values from food packaging materials from literature found styrene exposure was 0.122 μg/kg bw/day when using the 90th percentile migration values and 0.169 μg/kg bw/day when using the maximum migration values. These estimated intakes are below PMTDI of 40 μg/kg bw/day, which was established by JECFA. The authors conlcuded that styrene is not a concern for Irish children.[66]

56. CFS conducted a risk assessment study about the safety of cup noodle containers in 2009. In the study, among other tests, a total of 16 samples made of PS, expanded polystyrene (EPS), or contained PS contact surface which included 11 containers and 5 lids, were tested for styrene monomer. The levels of residual styrene monomer ranged from not detected to 1000 mg/kg (0.1 weight percent) which were within the limit, 0.5 weight percent of total residual styrene monomer, as stipulated by the USFDA.[67]

Standards/regulatory limits of styrene in food

57. There is no Codex and local standards for styrene in food. As for food contact materials, the EU has not set SML for styrene monomer from plastic food contact materials. The USFDA required that PS and rubber-modified PS should contain no more than 0.5 weight percent (5000 mg/kg) of total residual styrene monomer.[68]

V. Phthalates

58. Phthalates are a group of chemicals used as plasticisers, which provide flexibility and durability to plastics such as polyvinyl chloride (PVC). Phthalates are dialkyl or alkyl aryl esters of 1,2-benzenedicarboxylic acid.[69] Of various phthalates, di(2-ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP) and butylbenzylphthalate (BBP) have received the most regulatory and scientific attention due to their toxic effects on reproduction and development in experimental animals.

Uses

59. Phthalates are produced in the millions of tons annually worldwide and used in a wide variety of consumer and industrial products. Plastics such as PVC that contain phthalates are commonly used in applications that include building materials, clothing, cosmetics, perfumes, food packaging, toys, and vinyl products (e.g., flooring, shower curtains, and rain coats); and in medical applications that include blood transfusion bags and tubing, intravenous fluid bags and tubing, and other medical devices. Phthalates are also found in lubricating oils, solvents, and detergents.[70] PVC is also used in food contact materials include bottles, cling films, cap seals for canned and bottles food, hose and tubing for transport of soft drinks and beer, closures and can linings, etc.[71]

Sources of exposure

60. Phthalates may be present in food, either due to migration from food contact materials or due to their widespread presence as an environmental contaminant which can be found in air, water, soil and food. It appears that the major source of exposure to the most common phthalate, DEHP, for the general population is via food. Other potential exposure routes includes occupational exposure, exposure through the use of toys and childcare articles by children, use of cosmetic products by the general population and use of PVC devices by patients undergo medical procedures.[72,73]

Toxicity

61. Phthalates including DEHP, BBP DBP, di-isononyl phthalate (DINP), and di-isodecyl phthalate (DIDP) are metabolised and excreted quickly and do not accumulate in the body. They have low acute toxicity.[74,75,76,77,78] The developing male reproductive tract appears to be the most sensitive endpoint, although effects on the liver, kidneys, lungs, and blood clotting are also of concern. In animal tests considered relevant to humans, several phthalates, including DEHP, DBP, BBP, and perhaps DINP, interfere with male reproductive tract development and are toxic to cells in the testes responsible for assuring normal sperm and hormone production.[79]

62. Available data showed that DEHP and BBP are not genotoxic. IARC classified DEHP as Group 2B, i.e. possibly carcinogenic to humans, and BBP as Group 3, i.e. not classifiable as to carcinogenicity to humans.[80,81] No evaluation was given to other phthalates by IARC. The USEPA has determined that DBP is not classifiable as to human carcinogenicity based on inadequate evidence in both humans and animals.[82]

63. The safety of certain phthalates that are more relevant to human exposure have been evaulated by international and national authorities. During the review of Guidelines for Drinking-water Quality, the WHO in 2003 allocated a TDI of 0.025 mg/kg bw for DEHP, based on a no-observable-adverse-effect-level (NOAEL) of 2.5 mg/kg bw/day for peroxisomal proliferation in the liver in rats, using an uncertainty factor of 100 for inter- and intra species variation.[83]

64. The five phthalates were evaluated by EFSA for their use in food contact materials in 2005. TDIs of 0.05 mg/kg bw for DEHP, 0.5 mg/kg bw for BBP, 0.01 mg/kg bw for DBP, and 0.15 mg/kg bw for DINP and DIDP, respectively, were allocated by EFSA.[70,84,85,86,87]

Endocrine disrupting effects

65. Some epidemiological studies have suggested that phthalate exposure, especially during the prenatal period, induces a number of adverse effects in humans, such as developmental and behavioral abnormalities.[88,89] A study suggested that the endocrine disrupting activities of phthalates may relate to their alkyl chain length and hydroxylation of phthalates that have a significant impact on binding ERs and peroxisome proliferator-activated receptors (PPARs).[90]

66. Evidence from recent studies suggested DEHP acts as thyroid receptor antagonist. An epidemiological study showed that adults exposure to phthalates and BPA was found to inversely affect thyroid function. High levels of the metabolites of DEHP were found to have the strongest negative effect on thyroid function. However, the results obtained from adults were contrary to those obtained from adolescents in the 12 to 19 age groups. In fact, a positive association was found between DEHP and levels of thyroid hormones in young participants.[91] The reason

for this inconsistency will have to be explored in future studies.

67. In addition, a study showed that in adult male humans, concentrations of phthalate metabolites are correlated with abdominal obesity and insulin resistance.[92] However the report of the DG Environment commented that the study design was cross-sectional and the association requires examination in a longitudinal study.[93]

68. Two key studies conducted in the U.S. among young boys provide good evidence of associations of irreversible effects in the form of altered hallmarks of sexual differentiation with elevated phthalate exposures during fetal life. A summary score of urinary phthalate metabolite levels showed associations with shorter anogenital index (AGI). The relationships of shorter AGI with other health outcomes, including testicular descent and genital morphology were also investigated. The likelihood of incompletely descended testes was strongly related to shorter AGI, as was the proportion of boys with a scrotum categorized as small and with a small penis size. Neurodevelopment and metabolic endpoints are emerging areas of concern in relation to phthalate exposure, since studies of prenatal exposure have found associations with phthalate exposure and attention deficit hyperactivity disorder (ADHD)-link symptoms and lowered IQs, and exposure has been implied as a risk factor for obesity, insulin resistance and diabetes by others.[29]

69. The Federal Institute for Risk Assessment (BfR) of Germany opined that there are still no reliable studies available about the effects on humans of exposure to low doses of phthalates so far. There is a need for more research to characterise the health risk of current phthalate exposure for man in a more precise manner. The main question is whether the impact of individual substances is amplified in phthalate

compounds. Animal experimental studies with individual phthalates and mixtures indicate an additive effect in the disruption of testosterone formation in animal progeny.[94]

Levels in food and dietary exposure estimation

70. Contamination of food by DEHP can occur during processing, handling, transportation and packaging of food and via "secondary" food storage articles. During processing, food may be contaminated from PVC tubing and other process equipment containing DEHP. For example, transfer of DEHP from tubes to milk during different operations in dairies may occur. DEHP may be used in lubricants in the food processing industry e.g. in slaughter-houses. Contamination of food products with DEHP can occur via polymer and non-polymer components of food packaging materials, for instance printing ink used for flexible food packaging, glues used for paper and plastics, in aluminium foil-paper laminates and closure seal in bottles, DEHP is often present in paper and board packaging and at generally low concentrations (typically less than 10 mg/kg) in foods packaged in paper and board.[70]

71. Data from the U.S. showed the levels of DEHP in food appear to be generally low (< 1 ppm) but certain processed and/or fatty items may be higher.[73] In a sampling of a wide variety of foods, the highest levels were found in milk (31.4 mg/L, fat basis, about 1.02 mg/L on product basis) and cheese (35 mg/kg, fat basis). In a study of the migration of DEHP from plastic packaging films, it was found in tempura (frying) powder (0.11–68 mg/kg), instant cream soup (0.04–3.1 mg/kg), fried potato cake (0.05–9.1 mg/kg), and orange juice (0.05 mg/kg).[95] According to the Rapid Alert System for Food and Feed (RASFF) of the EC in 2011, high levels (from several hundred ppm to over 1000 ppm) of DEHP or DINP were found in some

imported oil based sauces (e.g. curry sauce). It might be caused by the migration of phthalates from lids of glass jars.[96]

72. A study of the UK Food Safety Agency (UKFSA) looked for the presence of phthalates in food samples collected as part of the 2007 TDS. Of the 26 different phthalates that were looked for in the samples, only eight were detected, including DEHP, BBP and DBP. It found that intakes of DEHP, BBP and DBP estimated from the levels in the TDS food samples, were all below their respective TDIs set by EFSA and did not indicate a risk to human health from dietary exposure.[97]

73. To assess the risk from total dietary exposure to phthalates (i.e. from the combination of all phthalates in the diet), the Committee of Toxicology of UK assumed that the toxic effects of each individual phthalate would be similar, and that the combined toxic effect for a mix of phthalates could be estimated by adding together the exposure estimates for individual compounds. The Committee compared an estimate of the highest total exposures to all phthalates with the lowest TDI for any of the individual compounds (which was for DBP). The estimated total phthalate exposure was approximately twice the TDI for DBP. The Committee considered this did not indicate a concern for health since, i) most of the phthalates are less potent than DBP, ii) the TDI for DBP was likely to be very conservative, and iii) DBP accounted for only approximately 5% of the total exposure to phthalates. Overall the Committee concluded that levels of phthalates found in samples from the 2007 TDS did not indicate a risk to human health from dietary exposure alone. However other, non-dietary, sources of exposure would need to be considered in a full risk assessment for phthalates.[97]

Standards/regulatory limits of phthalates in food and food contact materials

Food

74. There is no Codex standard for phthalates such as DEHP in food. Phthalates cannot be added into food. The CFS has set action levels of 1.5 mg/kg for DEHP, 9 mg/kg for DINP/DIDP (as the sum of the substances) and 0.3 mg/kg for DBP in food as a result of the DEHP-tinted clouding agent incident originated in Taiwan in May 2011. The CFS has included phthalates in Hong Kong's routine food surveillance after the incident.

Food contact materials

75. JECFA in 1988 evaluated DEHP and recommended that human exposure to this compound in food be reduced to the lowest level attainable. The Committee considered that this might be achieved by using alternative plasticisers or alternatives to plastic material containing DEHP.[98]

76. As additives in food contact materials, the EU law limits the use of certain phthalates in plastics that come into contact with food, with specific restrictions on the maximum amount that can migrate into foods (i.e. SML). In additional of SML, there are some requirements on the use of the phthalates. For example, DEHP can only be used as plasticiser in repeated-use materials and articles contacting non-fatty foods and technical support agent in concentrations up to 0.1 % in the final product. For DINP and DIDP, they can be used in both repeated use materials and articles and single-use materials and articles contacting non-fatty foods except for infant formulae and follow-on formulae or processed cereal-based foods and baby foods for infants and young children.[99]

VI. Organotins

77. Organotins or stannanes are a group of chemical compounds based on tin with hydrocarbon substituents. Organotins are classified as R_4Sn, R_3SnX, R_2SnX_2, and $RSnX_3$. In compounds of industrial importance, R is usually a butyl, octyl, or phenyl group and X is a chloride, fluoride, oxide, hydroxide, carboxylate, or thiloate.[100]

Uses

78. Tri-substituted compounds (e.g. tributyltin (TBT) and triphenyltin (TPT)), have been used extensively as biocides in wood preservatives, in antifouling paints for boats and as pesticides. They are the main source of organotins in food. Mono- and di-substituted organotins (e.g. monomethyltin (MMT), dimethyltin (DMT), dibutyltin (DBT), mono-n-octyltin (MOT) and di-n-octyltin (DOT)) are generally used in mixtures in various amounts as PVC stabilisers, and dialkyltins have been approved as PVC stabilisers for food contact materials.[101,102]

Sources of exposure

79. Exposure to organotins such as TBT compounds mainly occurs in the occupational setting.[103] For general population, the main source of organotins is dietary exposure from fishery products as organotins tend to bioaccumulate through the food chain (in particular in fish and seafood). Consumers are also exposed to organotins from other sources, e.g. pesticides, additives used in plastics, other food contact materials and consumer products.[102] Organotins occur in food from environmental contamination and from food contact materials. As they are loosely bound to the food contact material they are at high risk of migrating upon contact with foods.[101]

Toxicity

80. Animal studies showed organotins have median acute toxicity. The critical toxicological endpoint for risk assessment for organotins was considered to be immunotoxicity. TBT and TPT affect the immune system, resulting in impaired function. They have also been found to cause reproductive effects and developmental toxicity in animal studies. TBT and TPT caused masculinization in female snails (i.e. "imposex", characterised by the development of additional male sex organs on females) and in fish at low concentrations (1 ng/L in water), suggesting that these compounds are endocrine disrupters. Reproductive and developmental toxicity in rodents at relatively low doses (around 1 mg/kg bw/day) further supports the endocrine activity of organotins. [102]

81. TBT and TPT have not been evaluated for carcinogenicity by IARC. USEPA has evaluated tributytin hydroxide (TBTH) as “cannot be determined” for its carcinogenicity and triphenyltin hydroxide (TPTH) as category B2, “probable human carcinogen”. [104,105] TBT and TPT do not present a genotoxic hazard. [102]

82. EFSA assessed organic tin compounds in 2004. As these compounds have a similar profile of action and potency in terms of immunotoxicity in rats, a group TDI of 0.25 μg/kg bw for TBT, DBT, TPT and DOT compounds was established (based on TBT oxide molecular mass, this group TDI is 0.1 μg/kg bw when expressed as Sn content or 0.27 μg/kg bw when expressed as TBT chloride). [102]

Endocrine disrupting effects

83. Some evidence indicated that organotins exposure might be associated with obesity and diabetes in humans.[106,107] An animal study demonstrated TBT and TPT bind with high affinity to the peroxisome proliferator-activated receptor gamma (PPARγ) and the retinoid X receptors (RXR), receptors that affect adipocite differentiation, energy storage and nuclear receptor signaling.[108] A review study suggested that humans, who have been exposed to obesogenic chemicals, might be pre-programmed to store increased amounts of fat, resulting in a lifelong struggle to maintain a healthy weight and exacerbating the deleterious effects of poor diet and inadequate exercise.[109]

84. A number of animal studies suggested that TPT affect glucose regulation and may induce diabetes. However, a review by National Toxicity Program (NTP) of the U.S. stated that there are currently not enough data and no epidemiological studies available that evaluate the association of organotin exposure with diabetes, adiposity, or health effects related to metabolic syndrome.[107]

Levels in food and dietary exposure estimation

85. EFSA's intake calculations based on fish and seafood consumption in Norway, taken as paradigm of high consumption in Europe showed that the combined TBT, DBT and TPT intake for the general population is below the TDI. The intakes for high consumers, calculated on median and mean concentrations were 0.037 and 0.17 μg/kg bw/day, respectively, which represents approximately 15 % and 70 % of the group TDI. EFSA noted that in few cases where seafood contamination with organotins is high, the TDI might be exceeded for example in the case of consumption of contaminated fish, mussels and other marine animals from the vicinity of harbours

and heavily used shipping routes. [102]

86. A study of the butyltin residues in fishes caught along the west coast of Taiwan, found the total concentrations of DBT plus TBT in the muscle or the internal organ were lower than the tolerable average residue level (TARL) of 175.4 ng/g wet weight. TARL is the level in seafood that is tolerable for the average consumer with an average body weight of 60 kg based on the daily consumption amount of seafood of the local population and the TDI of 0.25 μg/kg bw. Therefore, the study concluded that butyltin levels in fish from Taiwanese markets are not a matter of concern for public health. [110]

87. A Portuguese study showed that the levels of TBTs in edible parts of fish, crustaceans and cephalopods collected in markets are in the lower range of that reported for these animal groups from other locations (i.e. below 30 ng/g wet weight). In contrast, moderate to high concentrations have been observed in bivalves (up to 275 ng TBT/g wet weight). While most samples showed TBT plus DBT levels below the TARL, which might indicate low risk for consumers. However, four bivalve samples displayed butyltin levels above TARL, thus indicating that higher bivalve consumer groups might be at risk. [111]

Standards/regulatory limits of organotins in food and food contact materials

Food

88. One of the organotin compounds, TPTH, is a fungicide. Currently there are no Codex Maximum Residue Limits (MRLs) for pesticides established for residues of TPTH in plant or animal commodities. [112] In the U.S., there are MRLs of TPTH set for certain commodities including potato, pecan, sugar beet, and some animal products such as meats, fats and internal organs. In Hong Kong, MRLs of TPTH

have been set in certain food items under the Pesticide Residues in Food Regulation.[113]

Food contact materials

89. Some organotins are authorised by the USFDA as indirect food additives for various applications or approved by the EU as food contact materials.[99, 114]

VII. Nonylphenol (NP)

90. NP is a generic term used to describe a complex commercial mixture of mainly nonyl-substituted phenol, a type of alkylphenol. NP has many isomers that are straight or branched. The branched isomer, 4-nonylphenol (4-NP) is mainly detected in the environment and has relatively strong endocrine disrupting effects.[115] The addition of ethoxyl groups to the parent compound produces ethoxylates nonylphenol ethoxylates (NPEs), which are used to produce industrial surfactants. Alkylphenol is the second largest group of nonionic surfactants in commercial production, of which NPEs account for approximately 80 percent. NP is the predominant environmental biodegradation product of NPEs. It is ubiquitous and moderately persistent.[116]

Uses

91. The primary uses of NP include being a building block of NPEs, nonionic surfactants that reduce surface tension of liquids used in lubrication, defoaming agents, scouring fibers, emulsifiers, wetting and de-wetting agents, dyes and other products. NP is also used to produce an antioxidant, tris(nonylphenol)phosphate, to stabilise plastics and rubber.[115]

Sources of exposure

92. NP can enter the human body either by the inhalation of air containing NP, ingestion of contaminated water or food, or by dermal contact with NP-containing consumer products.[117] NP is taken up from water and sediment by aquatic organisms. A potential pathway for human exposure to NP is through consumption of market seafood items. While not a significant source of NP in the environment, unreacted NP in plastic may result in direct human exposures when the chemical leaches out of plastic in close contact with foods.

Toxicity

93. The acute toxicity of NP is low by the oral route.[118] The major toxic effects of NP found in animal studies are reproductive and developmental effects. Some animal studies showed NP could adversely affect the immune system and brain development.[115] Available *in vitro* studies suggest that NP is not genotoxic. No information is available on the carcinogenicity of NP.[117] IARC has not evaluated the carcinogenicity of NP. A TDI of 5 μg/kg bw has been proposed by the Danish Institute of Safety and Toxicology.[119]

Endocrine disrupting effects

94. No human data of endocrine disrupting effects of NP are available. NP and some of its degradation products have been shown to have estrogenic activities in a number of *in vitro* and *in vivo* assays. Adverse effects which are thought to be linked to NP's estrogenic activity include effects on the testes, including decreased sperm production, increased uterine weight, suggesting that NP may affect female reproduction, altered development of the brain region responsible for male and female behaviour, hyperactivity in juvenile animals and animals exposed before birth due to

effects on the development of regions of the brain.[116] However, studies showed NP was estrogenic only at relatively high dose levels and its potency in those estrogenic activities ranged from 3 to 6 orders of magnitude less than that of estradiol.[120]

Levels in food and dietary exposure estimation

95. Seafood including fish and shellfish are the most common food samples being investigated for their NP concentrations. The NP concentrations in seafood from various locations including Italy Mainland China, Taiwan, Singapore and U.S. ranged from 3.3 to 1 431 μg/kg.[121,122,123,124,125,126]

96. NP was also found in a variety of other food items. A study conducted in Germany found that the widely varying concentrations of NP independent of the fat contents and the packaging materials of the food samples (e.g. butter (14.4 μg/kg), lard (10.2 μg/kg), or liver sausage (13.0 μg/kg) but also in non fatty food like marmalade (7.3 μg/kg), apples (19.4 μg/kg), tomatoes (18.5 μg/kg)) implied that NPs get into food on miscellaneous pathways and at different stages of food production such as from NPEs which are used as nonionic surfactants in disinfectants and cleaning agents or as emulsifiers in pesticide formulations. Another source might be plastic packaging materials from which NPs, used for example in tris(nonylphenol)phosphite as antioxidant, could migrate into food.[127]

97. Limited data showed the estimated dietary exposure to NPs of New Zealand, German and Taiwan adults were 3.29 μg/day (N=1 030), 7.5 μg/day (N=25 000) and 31.40 μg/day (N=3 915), respectively.[124, 127, 128] Although these estimated exposure values varied significantly, they did not exceed the TDI of 5 μg/kg bw (300μg/day for a 60-kg adult) proposed by the Danish Institute of Safety and Toxicology. For adults,

rice in Taiwan was the major contributor which accounted for 21.46% daily intake of NP, followed by aquatic products and livestock which accounted for 17.97% and 17.38% of TDI, respectively.[124] UKFSA found migration from two PVC cling film samples in its study had NP migration of about 0.2 to 0.8 mg/kg into cheese and 0.3 to 0.6 mg/kg into cake. It commented that migration of PVC cling films has the potential to result in exposures of NP approaching or exceeding the proposed TDI.[119]

Standards/regulatory limits of NP in food and food contact materials

98. There is no international or local standard for NP in food at present. As for food contact materials, certain surfactants including sodium ethylene ether of NP are approved indirect food additives for use as adhesive in the U.S..[129] NP itself is not authorised for use in food contact plastics in EU although it may be present as an impurity or a breakdown product of alkylphenol ethoxylates or tris(nonylphenyl)phosphite. No EU SML has been assigned to NP.[99]

SUMMARY AND RECOMMENDATIONS

99. This study discussed the toxicity including endocrine disrupting effects of selected potential EDCs as well as the health risks associated with dietary exposure of these chemicals according to literature reviewed. Available data from different countries on organochlorine pesticides (including DDT, HCB and mirex), dioxins and dioxin-like PCBs, BPA, styrene, phthalates, organotins and NP, and local risk assessment studies on DDT and dioxins and dioxin-like PCBs showed that dietary exposure of general population to these chemicals were below their respective health-based guidance values (e.g. TDI).

100. The exposures to organotins and NP of some consumers might exceed the

TDIs occasionally under specific conditions although available data from overseas found that the exposures to these chemicals of both average and high consumers are well below the TDIs. For example, EFSA noted that, in a few cases, high consumers of highly contaminated seafood may have exposure to organotins exceeding the TDI and the UKFSA found that the migration of NP from certain PVC cling films into high fat food products has the potential to result in exposures of NP approaching or exceeding the proposed TDI. Nevertheless, transient excursion above the TDI would be unlikely to cause health consequences provided that the average intake does not continuously exceed the TDI which emphasises on a lifetime exposure.

101. Although a number of animal studies showed certain chemicals have potential endocrine disrupting activities, there are not enough data on their endocrine disrupting effects in humans, especially through dietary exposure. At present, endocrine disrupting effects of chemicals in human are not clearly clarified through experimental data and epidemiological studies. International and national authorities are in the process of screening potential EDCs for setting research and management priority. To ensure food safety, CFS will keep in view the latest international risk assessments and management options on potential EDCs in food and take suitable follow-up actions where appropriate.

ADVICE TO TRADE

- Food traders should ensure that food on sale in Hong Kong complies with relevant regulations and is fit for human consumption.
- Manufacturers and suppliers of food contact materials should adopt good manufacturing practices and make sure that their products comply with recognised standards, i.e., standards stipulated by the European Commission

(EC), the U.S. Food and Drug Administration (USFDA), and the Ministry of Health (MOH) of the People's Republic of China.

ADVICE TO PUBLIC

- Maintain a balanced and varied diet so as to attain a good health and avoid excessive exposure to contaminants from a small range of food items, such as seafood, especially bivalves, as they generally contain higher level of environmental contaminants such as some EDCs and metallic contaminants.
- Buy food and food contact materials (including food packaging, containers and tableware) from reliable suppliers.
- When using plastic food contact materials, always follow manufacturer's instructions and pay attention to the suitability of the product for holding hot, fatty or acidic foods, or for use in microwave oven, etc. Misuse of these products may cause the migration of potential EDCs from the plastic materials to food.

REFERENCES

[1] WHO/IPCS. Global assessment of the state-of-the-science of endocrine disruptors. WHO/PCS/EDC/02.2. 2002. Available from URL:
http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html

[2] The Environment Directorate-General of the European Commission. Endocrine Disrupters Website. [Cited 3 April 2012]. Available from URL:
http://ec.europa.eu/environment/endocrine/index_en.htm

[3] Wuttke W, Jarry H, and Seidlovα-Wuttke D. Definition, classification and mechanism of action of endocrine disrupting chemicals. Hormones 2010; 9(1): -15
Available from URL:http://hormones.gr/pdf/HORMONES%202010%209-15.pdf

[4] Labelle C. Endocrine Disruptors update. Government of Canada. 2000. Available from URL: http://publications.gc.ca/Collection-R/LoPBdP/BP/prb0001-e.htm

[5] Australia Government, Department of Health and Aging NICNAS. Endocrine Disrupting Chemicals (EDCs). NICNAS [Cited 5 April 2012]. Available from URL:
http://www.nicnas.gov.au/international/Endocrine_Disrupting_Chemicals.asp

[6] EC DG Environment. Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption - preparation of a candidate list of substances as a basis for priority setting – Final Report 2000. Available from URL:
http://ec.europa.eu/environment/docum/pdf/bkh_main.pdf

[7] The Ministry of the Environment, Government of Japan Strategic Programs on Environmental Endocrine Disruptors '98 (SPEED '98). [Cited 5 Apirl 2012]. Available from URL: http://www.env.go.jp/en/chemi/ed/speed98/sp98t3.html

[8] USEPA. Endocrine Disruptor Screening Program (EDSP). [cited 5 April 2012]. Available from URL: http://www.epa.gov/endo/

[9] Government of Canada. – Order Amending Schedule I to the Hazardous Products Act (bisphenol A).. Vol 144, No. 7. March 31 2010. Available from: URL:
http://www.gazette.gc.ca/rp-pr/p2/2010/2010-03-31/html/sor-dors53-eng.html

[10] European Commission. Directives. Commission Directive 2011/8/EU of 28 January 2011. Amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles. Official Journal of the European Union. 2011. Available from: URL:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:026:0011:0014:EN:PDF

[11] Ministry of Health of the people's Republic of China 衛生部工業和資訊化部商務部工商總局質檢總局食品藥品監管局公告. 2011 年 第 15 號. 23 May 2010. [Article in Chinese] Available from URL:http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohwsjdj/s7891/201105/51866.htm

[12] Qiu YW, Zhang G, Guo LL, Cheng HR, Wang WX and Li XD. Current status and historical trends of organochlorine pesticides in the ecosystem of Deep Bay, South China. Estuarine, Coastal and Shelf Science 2009;85:265-272.

[13] Peng XZ, Wang ZD, Mai BX, Chen FR, Chen SJ, Tan JH, Yu TY, Tang CM, Li KC, Zhang G, and Yang C, Temporal trends of nonylphenol and bisphenol A contamination in the Pearl River Estuary and the adjacent South China Sea recorded by dated sedimentary cores. Science of the Total Environment 2007; 384:393-400.

[14] United Nations Environment Programme. Stockholm Convention on Persistent Organic Pollutants (POPs). Geneva, Secretariat of the Stockholm Convention. [cited at 24 Aug 2011] Available from URL: http://chm.pops.int/

[15] CDC. Forth National Report on Human Exposure to Environmental Chemicals. Organochlorine pesticides. [cited 30 March 2012] Available from URL:
http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf

[16] Becker S, Halsall CJ, Tych W, Kallenborn R, Schlabach M, and Manø S. Changing sources and environmental factors reduce the rates of decline of organochlorine pesticides in the Arctic Atmosphere. Atmosphere Chemistry and Physics 2009; 9:515-540.

[17] WHO. Chlordane. Pesticide residues in food: evaluations Part II Toxicology. Geneva: WHO; 1986. Available from URL:http://www.inchem.org/documents/jmpr/jmpmono/v86pr03.htm

[18] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 79. Some Thyrotropic Agents Summary of Data Reported and Evaluation. France: IARC; last updated 2001. Available from URL: http://monographs.iarc.fr/ENG/Monographs/vol79/volume79.pdf

[19] WHO. The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009. Available from URL:

http://www.who.int/ipcs/publications/pesticides_hazard_2009.pdf

[20] WHO. Pesticide residues in food: DDT(para,para'-Dichlorodiphenyltrichloroethane) (addendum). Geneva: WHO; 2000. Available from URL: http://www.inchem.org/documents/jmpr/jmpmono/v00pr03.htm

[21] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 53. Occupational Exposures in Insecticide Application, and Some Pesticides-Summary of Data Reported and Evaluation. France: IARC; last updated 1999. Available from URL: http://monographs.iarc.fr/ENG/Monographs/vol53/volume53.pdf

[22] Toxicological Profile for Hexachlorobenzene. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. 2002. Available from URL: http://www.atsdr.cdc.gov/ToxProfiles/tp90.pdf

[23] USEPA. Integrated Risk Information System. Hexachlorobenzene (CASRN 118-74-1) [cited 29, March 2012]. Available from URL: http://www.epa.gov/iris/subst/0374.htm

[24] Toxicological Profile for Mirex and Chlodecone. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. 1995. Available from URL: http://www.atsdr.cdc.gov/toxprofiles/tp66.pdf

[25] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 20. Some Halogenated Hydrocarbons. Summary of Data Reported and Evaluation. France: IARC; last updated 1999. Available from URL: http://monographs.iarc.fr/ENG/Monographs/vol20/volume20.pdf

[26] USEPA. Integrated Risk Information System. Chlordecone (Kepone); CASRN 143-50-0. [cited 29, March 2012]. Available from URL: http://www.epa.gov/ncea/iris/subst/1017.htm

[27] USEPA. Integrated Risk Information System. Mirex (CASRN 2385-85-5) [cited 29, March 2012]. Available from URL:http://www.epa.gov/iris/subst/0251.htm

[28] ATSDR. Draft Toxicological Profile for Toxaphene. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. 2010. Available from URL: http://www.atsdr.cdc.gov/toxprofiles/tp94.pdf

[29] Evans R, Kortenkamp A, Martin O, mcKinlay R, Orton, F and Rosivatz E. State of the Art Assessment of Endocrine Disrupters. 2nd Interim Report. Project Contract number 070307/2009/550687/SER/D3. Part 1. Summary of the State of the Science. 2011. EC Environment. Available from URL: http://ec.europa.eu/environment/endocrine/documents/4_Annex%202%20Summary%20of%20Exper%20Consultations%20V2.pdf

[30] Chevrier J, Eskenazi B, Holland N, bradman A, and Barr DB. Effects of Exposure to Polychlorinated Biphenyl and Organochlorine Pesticides on Thyroid Function during Pregnancy. American Journal of Epidemiology 2008;168(3); 298-310.

[31] Roman GC. Autism: Transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. Journal of the Neurological Science 2007;62:15-26.

[32] Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, Calderon N, Eskenazi B. Organophosphate Pesticides Exposure and Attention in Yong Mexican-American Children: the CHAMACOS Study. Environmental Health Perspective 2010;118:1768-74.

[33] Ribas-Fito N, Torrent M, Carrizo, Munoz-Ortiz L, Julvez J, Grimalt J and Sunyer J. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. American Journal of Epidemiology 2006;164: 955-962.

[34] Robert EM, English PB, Grether JK, Windham GC, Somberg L, and Wolff C. Maternal residence near agricultural pesticide applications and autism spectum disorders among children in the California Central Valley. Environmental Health Perspective 2007; 115:1482-1489.

[35] USFDA. Total Diet Study Market Basket 2004-1 through 2005-4. [cited 30 March 2012]. Available from URL: http://www.fda.gov/downloads/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/UCM291686.pdf

[36] CFS. Dietary exposure to DDT by Secondary School Students. Risk Assessment Report No. 24. 2006. Available from URL: http://cfs.fehd.hksarg/english/programme/programme_rafs/files/ddt.pdf

[37] Codex. Pesticide residues in Food and Feed. [cited 30 March 2012]. Available from URL: http://www.codexalimentarius.net/pestres/data/pesticides/index.html

[38] EU. Pesticide residue MRL. [Cited 30 March 2012]. Available from URL: http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=substance.selection&ch=1

[39] CFS. Refined Regulatory Framework for Pesticide Residues in Food in Hong Kong. [cited 10 April 2012]. Available from URL:

http://cfs.fehd.hksarg/english/whatsnew/whatsnew_fstr/whatsnew_fstr_21_Pesticide.html

[40] World Health Organization (WHO). Safety Evaluation on Certain Food Additives and Contaminants: Polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls; WHO Food Additives Series: 48. Geneva: WHO; 2002. Available from URL: http://www.inchem.org/documents/jecfa/jecmono/v48je20.htm

[41] European Food Safety Authority (EFSA). Results of the monitoring of dioxin levels in food and feed. EFSA Journal 2010: 8(3): 1385. Available from URL: http://www.efsa.europa.eu/fr/efsajournal/doc/1385.pdf

[42] FAO/WHO. Codex Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Foods and Feeds (CAC/RCP 62-2006). Available from URL: http://www.codexalimentarius.net/download/standards/10693/CXP_062e.pdf

[43] WHO. Exposure to dioxins and dioxin-like substances: A major public health concern. WHO 2010. Available from URL: http://www.who.int/entity/ipcs/features/dioxins.pdf

[44] International Agency for Research on Cancer (IARC). Summaries & Evaluations: Polychlorinated biphenyls (Group 2A). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7, 1987, p. 322. Available from URL: http://www.inchem.org/documents/iarc/suppl7/polychlorinatedbiphenyls.html

[45] IARC. Summaries & evaluations: Polychlorinated dibenzo-para-dioxins. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 69, 1997, p.33. Available from URL: http://www.inchem.org/documents/iarc/vol69/dioxin.html

[46] WHO IARC Monograph Working Group. Special Report: Policy – A review of human carcinogens – Part F: Chemical agents and related occupations. The Lancet Oncology 2009; 10(12): 1143-4.

[47] Mocarelli P, Gerthoux PM, Patterson DG, Milani S, Limonta G, Bertona M, Signorini S, Tramacere P, Colombo L, Crespi C, Brambilla P, Sarto C, Carreri V, Sampson EJ, Turner WE., Needham LL. Dioxin Exposure, from Infancy through Puberty, Produces Endocrine Disruption and Affects Human Semen Quality. Environmental Health Perspectives 2008; 116(1):73-77. Available fro URL: http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.10399

[48] USFDA. Questions & Answers About Dioxins and Food Safety. 2012 [cited 11 April 2012]. Available from URL: http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/DioxinsPCBs/ucm077524.htm

[49] CFS. The First Hong Kong Total Diet Study: Dioxins and Dioxin-like Polychlorinated Biphenyls (PCBs). 2012. Available from URL: http://cfs.fehd.hksarg/english/programme/programme_firm/files/Report_on_the_first_HKTDS_dioxin.pdf

[50] WHO. Dioxins and their effects on human health Fact sheet N°225. 2010. [cited 11 April 2012]. Available from URL: http://www.who.int/mediacentre/factsheets/fs225/en/

[51] EFSA (European Food Safety Authority). Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A. The EFSA Journal 2010; 8(9):1829. Available from: URL:http://www.efsa.europa.eu/en/efsajournal/pub/1829.htm

[52] FAO/WHO. Toxicological and Health Aspects of Bisphenol A. Report of Joint FAO/WHO Expert Meeting 2-5 November 2010 and Report of stakeholder meeting on Bisphenol A. 1 November 2010. Ottawa, Canada 2011. Available from: URL: http://whqlibdoc.who.int/publications/2011/97892141564274_eng.pdf

[53] Health Canada. Survey of Bispehnol A in Baby Food Products Prepackaged in Glass Jars with Metal Lids. March. 2009. Available from URL: http://www.hc-sc.gc.ca/fn-an/pubs/securit/bpa_survey-enquete-eng.php

[54] Consumer Union. Consumer Reports'Tests of Bisphenol-A (BPA) in Canned/Packaged Foods. Consumer Reports. 2009. Available from URL: http://buysafeeatwell.org/blog/2009/11/consumer-reports-test-of-bpa-in-canned-packaged-foods-december-2009.html

[55] Thomson BM, Grounds PR. Bisphenol A in canned foods in New Zealand: an exposure assessment. Food Additives and Contaminants 2005; 22(1):65-72.

[56] European Commission. Directives. Commission Directive 2011/8/EU of 28 January 2011 Amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles. Official Journal of the European Union. 2011. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:026:0011:0014:EN:PDF

[57] Ministry of Health of the People's Republic of China. GB 9685-2008: Hygienic standard for uses of

additives in food containers and packaging materials. 2009.

[58] WHO Europe. Air Quality Guidelines - Second Edition. Chapter 5.12-Styrene. 2010. [cited 13 April 2012] Available from URL:
http://www.euro.who.int/__data/assets/pdf_file/0018/123066/AQG2ndEd_5_12Styrene.pdf

[59] WHO. Environmental Health Criteria 26. Styrene. 1983. Available from URL:
http://www.inchem.org/documents/ehc/ehc/ehc26.htm#PartNumber:1

[60] WHO. Toxicological Evaluation of Certain Food Additives and Food Contaminants. WHO Food Additives Series no.19. 1982. Available from URL:
http://www.inchem.org/documents/jecfa/jecmono/v19je15.htm

[61] International Agency for Research on Cancer (IARC). Summaries & Evaluations: Styrene, Volume 82, 2002. Available from URL: http://www.inchem.org/documents/iarc/vol82/82-07.html

[62] World Health Organization (WHO). Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives: Styrene. 2001. Available from URL:
http://www.inchem.org/documents/jecfa/jeceval/jec_2204.htm

[63] Ministry of Health and Welfare of Japan. Interim Report Effects of Endocrine Disruptors on Human Health. 1998 Available from URL:
http://www.ffcr.or.jp/zaidan/ffcrhome.nsf/7bd44c20b0dc562649256502001b65e9/5e69e178bbad89414925681d001fa22d/$file/appendix-2.pdf

[64] Hirano, S.; Azuma, Y.; Date, K.; Ohno, K.; Tanaka, K.; Matsushiro, S.; Sakurai, T.; Shiozawa, S.; Chiba, M.; Yamada, T. Biological evaluation of styrene oligomers for endocrine-disrupting effects. Journal of the Food Hygienic Society of Japan 1999; 40:36-45.

[65] Steele DH, Thornburg MJ, Stanley JS, Miller RR, Brooke R, Cushman JR and Cruzan G. Determination of Styrene in Selected Foods. Journal of Agriculture Food Chemistry 1994; 42:1661-1665.

[66] Duffy E. and Gibney MJ. Use of a food-consumption database with packaging information to estimate exposure to food-packaging migrants: expoxidized soybean oil and styrene monomer. Food Additives and Contaminants 2007; 28(20):216-2

[67] CFS. Risk Assessment Report no 36. The Food Safety of Instant Cup Noodle Containers. 2009. Available from URL:
http://cfs.fehd.hksarg/english/programme/programme_rafs/programme_rafs_fc_01_21.html

[68] U.S. Food and Drug Administration (FDA). 21 CFR Ch. 1 Sub Ch. B, Sec. 177.1640: Polystyrene and rubber-modified polystyrene. Revised as of April 1 2007. Available from URL:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm\

[69] USEPA. Phthalates Teach Chemical Summary. 2007 [cited 24 Feb 2012] Available from URL:
http://www.epa.gov/teach/chem_summ/phthalates_summary.pdf

[70] EFSA. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to Bis(2-ethylhexyl)phthalate (DEHP) for use in food contact materials. Question N° EFSA-Q-2003-191. EFSA Journal 2005; 243 : 1-20. Available from URL: http://www.efsa.europa.eu/en/scdocs/doc/243.pdf

[71] Leadbitter J. Packaging Materials 5. Polyvinyl Chloride (PVC) For Food Packaging Applications. International Life Sciences Institute. June 2003. Available from URL:
http://www.ilsi.org.ar/biblioteca/ILSI_Europa_Monografias/RPPM5PVC[1].pdf

[72] USEPA. Technology Transfer Netwaor. Bis(2-ethylhexyl) phthalate (DEHP). 117-81-7. January 2000. Available from URL: http://www.epa.gov/ttnatw01/hlthef/eth-phth.html

[73] ATSDR. Toxicology Profile of Di(2-ethylhexyl)phthalate. Update. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. 2002. Available from URL:
http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=684&tid=65

[74] EU JRC. BIS (2-ETHYLHEXYL) PHTHALATE (DEHP) CAS No: 117-81-7 EINECS No: 204-211-0 RISK ASSESSMENT. 2008. Available from URL:
http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/5648/1/dehpreport042.pdf

[75] EU JRC. Union Risk Assessment Report, Benzyl Butyl Phthalate (BBP). CAS Nos: 85-68-7. EINECS Nos: 201-622-7. RISK ASSESSMENT. 2003. Available from URL:
http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/10948/1/benzylbutylphthalate report318.pdf

[76] EU JRC. Union Risk Assessment Report, Dibutylphthalte (DBP) EINECS No: 201-557-4. RISK ASSESSMENT. 2003. Available from URL:
http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/5681/1/EUR%2019840%20EN.pdf

[77] EU JRC. 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-“isononyl” phthalate (DINP) CAS No: 68515-48-0, 28553-12-0 EINECS No: 271-090-9, 249-079-5. RISK

ASSESSMENT. 2003. Available from URL: http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/5395/1/EUR%2020784%20EN.pdf

[78] EU JRC. 1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich and di-"isodecyl" phthalate (DIDP). CAS Nos: 68515-49-1 and 26761-40-0. EINECS Nos: 271-091-4 and 247-977-1. RISK ASSESSMENT. 2003. Available from URL: http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/5459/1/EUR%2020785%20EN.pdf

[79] Health Care Without Harm. Aggregate Exposures to Phthalates in Humans. July 2002. Available from URL:http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120502/02d-0325-c000018-02-vol1.pdf

[80] IARC. Some Chemicals in Industrial and Consumer Products, Food Contaminants and Flavourings, and Water Chlorination By-Products. VOL 101. April 2011. Available from URL: http://monographs.iarc.fr/ENG/Meetings/index1.php

[81] IARC 1999 International Agency for Research on Cancer (IARC) - Summaries & Evaluationns BUTYL BENZYL PHTHALATE (Group 3). 1999. Available from URL: http://www.inchem.org/documents/iarc/vol73/73-04.html

[82] USEPA Integrated Risk Information System Dibutylphthalate (DBP) (CASRN 84-74-2) Last updated 1987. Available from URL: http://www.epa.gov/iris/subst/0038.htm

[83] WHO. Di(2-ethylhexyl)phthalate in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality. 2003. Available from URL: http://www.who.int/water_sanitation_health/dwq/chemicals/di2ethylhexyphthalate.pdf

[84] EFSA. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related Butyl benzyl phthalate (BBP) for use in food contact materials Question N° EFSA-Q-2003-195. The EFSA Journal 2005; 241:1-14. Available from URL: http://www.efsa.europa.eu/en/efsajournal/doc/241.pdf

[85] EFSA. Scientific Document: Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to di-ButylPhthalate (DBP) for use in food contact materials. Question N° EFSA-Q-2003-192 EFSA Journal 2005; 242: 1-17. Available from URL: www.efsa.europa.eu/en/scdocs/scdoc/242.htm

[86] EFSA. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to Di-isononylphthalate (DINP) for use in food contact materials Question N° EFSA-Q-2003-194. EFSA Journal 2005; 244:1-18. Available from URL:http://www.efsa.europa.eu/en/efsajournal/doc/244.pdf

[87] EFSA. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to Di-isodecylphthalate (DIDP) for use in food contact materials Question N° EFSA-Q-2003-195. The EFSA Journal 2005; 245: 1-14. Available from URL: http://www.efsa.europa.eu/en/efsajournal/doc/245.pdf

[88] Engel SM, Zhu C, Berkowitz GS, Calafat AM, Silva MJ Niodovnik A and Wolff MS. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. Neutotoxicology 2009; 30:522-528.

[89] Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, Calafat AM and Wolff MS. Endocrine disruptors and childhood social impairment. Neurotoxicology 2011; 32: 261-267.

[90] Okamoto Y, Ueda K and Kojima N. Potential Risks of Phthalate Esters: Acquistion of Endocrine-disrupting Activity during Enviromental and Metabolic Processing. Journal of Health Science 2011; 57(6):497-503.

[91] Meeker JD and Ferguson KK. Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from NHANES 2007-08. Environmental Health Perspective 2011; 119: 1396-1402.

[92] Stahlhut RW, van Wijngaarden E, Dye TD, Cook S and Swan SH. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environmental Health Perspective 2007; 115(6):876-82.

[93] Evans R, Kortenkamp A, Martin O, Mckinlay R, Orton F and Rosivatz E. State of the Art Assessment of Endocrine Disrupters. 2nd Interim Report. Part 1 Summary of the State of the Science. The Directorate-General for the Environment. Draft 2011. Available from URL: http://ec.europa.eu/environment/endocrine/documents/summary_state_science.pdf

[94] BfR. Press release. Endocrine disruptors: Substances with harmful effects on the hormone system. 2010. [Cited March 9 2012]. Available from URL: http://www.bfr.bund.de/cd/50525.

[95] WHO. Di(2-ethylhexyl)phthalate in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality. 2003. Available from URL:

http://www.who.int/water_sanitation_health/dwq/chemicals/di2ethylhexyphthalate.pdf
[96] EUROPA. RASFF Portal - Online searchable database. Available from URL: http://ec.europa.eu/food/food/rapidalert/rasff_portal_database_en.htm
[97] Committee on Toxicity. COT Statement on Dietary Expososure to Phthalates – Data from the Total Diet Study (TDS). 2011. Available from URL: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201104
[98] JECFA. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. Di(2-ethylhexyl)phthalate. 1988. Available from URL: http://www.inchem.org/documents/jecfa/jeceval/jec_766.htm
[99] EU. COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Available from URL: http://www.nicnas.gov.au/Publications/CAR/PEC/PEC32/PEC_32_Full_Report_pdf.pdf
[100] WHO. Environmental Health Criteria 15. Tin and Organotin Compounds. 1980. Available from URL: http://www.inchem.org/documents/ehc/ehc/ehc015.htm
[101] Technical University of Denmark. DTU Food. National Food Institute. Organotin compounds in food contact materials. 2010. [cited March 8 2012]. Available from URL: http://www.food.dtu.dk/Default.aspx?ID=20917
[102] EFSA. Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission to assess the health risks to consumers associated with exposure to organotins in foodstuffs (Question N° EFSA-Q-2003-110). The EFSA Journal 2004; 102:1-119. Available from URL: http://www.efsa.europa.eu/en/efsajournal/doc/102.pdf
[103] Scottish Environment Protection Agency. Tributyltin compounds. [cited 27 Feb 2012]. Available from URL: http://apps.sepa.org.uk/spripa/Pages/SubstanceInformation.aspx?pid=167
[104] USEPA. Toxicological review: Tributyltin oxide. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington DC. 1997.
[105] USEPA. Triphenyltin hydroxide. RED: EPA 738-R-99-010. U.S. Environmental Protection Agency, Washington DC. 1990.
[106] Muncke L. Endocrine disrupting chemicals and other substances of concern in food contact materials: an updated review of exposure, effect and risk assessment. Journal of Steroid and Biochemistry Molecular Biology 2011; 127(1-2):118-27. Available from URL:
[107] NTP. NIEHS Environmental Factor Article: NTP workshop investigates links between chemicals and obesity Organotins and Phthalates (version updated January 5, 2011). Available from URL: http://ntp.niehs.nih.gov/ntp/ohat/diabetesobesity/Wkshp/OrgantinsPhthalatesDraftLiteratureReviewV3formatted.pdf
[108] F. Grun and B Blumberg, Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. Endocrinology 2006; 146(6) 50-55.
[109] Janesick A and Blumberg B. The Role of Environmental Obseogens in the Obesity Epidemic. Endocrine Update 2011; 30(4) 383-399.
[110] Chen CH, Huang KM, Ho CH, Chang CF and Liu SM. Butyltin Compounds in Fishes Commonly Sold in Taiwan Markets. Journal of Food and Drug Analysis 2008; 16(6) 54-66. 2008 Available from URL:http://www.fda.gov.tw/files/publish_periodical/P008-066.pdf
[111] Santos MM, Enes P, Reis-Henriques MA, Kuballa J, FilipeL,Castro C, Vieira MN. Organotin levels in seafood from Portuguese markets and the risk for consumers. Chemosphere 2009; 75(5):661-666.
[112] Codex. Codex persticide residues in food online database. [cited 20 March 2012]. Available from URL: http://www.codexalimentarius.net/pestres/data/index.html
[113] CFS. Consulatation Document. Refined Regulatory Framework for Pesticide Residues in Food in Hong Kong. July 2011. Available from URL: http://cfs.fehd.hksarg/english/whatsnew/whatsnew_fstr/files/20110713-20110919_Public_Consultation paper(e).pdf
[114] USFDA. CFR - Code of Federal Regulations Title 21. [cited 20 March 2012]. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
[115] Environmental Health Department Ministry of the Environment Government of Japan. Report on the Test Results of Endocrine Disrupting Effects of Nonylphenol on Fish (Draft). 2001. Available from URL: http://www.oecd.org/dataoecd/7/4/2460701.pdf
[116] California Environmental Protection Agency. Toxicology Profile for Nonlyphenol 2009. Available from URL: http://www.opc.ca.gov/webmaster/ftp/project_pages/MarineDebris_OEHHA_ToxProfiles/Nonylphenol%20Final.pdf
[117] EU JRC. 4-NONYLPHENOL (BRANCHED) AND NONYLPHENOL CAS Nos: 84852-15-3 and

25154-52-3 EINECS Nos: 284-325-5 and 246-672-0. Summary risk assessment. 2002. Available from URL: http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/SUMMARY/4-nonylphenol_nonylphenolsum017.pdf

[118] USEPA. Hazard Characterization Document. Screening-Level Hazard Characterization. Alkylphenols Category. 2009. Available from URL: http://www.epa.gov/chemrtk/hpvis/hazchar/Category_Alkylphenols_Sept2009.pdf

[119] Bradley EL. Nonylphenol in food contact plastics and migration into foods. FSA, London FD 09/05. 2010.

[120] WHO/IPCS/IRA. Integrated Risk Assessment: Nonylphenol. Case Study Report Prepared for the Integrated Risk Assessment: Nonylphenol. WHO/UNEP/ILO International Programme on Chemical Safty. 2004. Available from URL: http://www.who.int/ipcs/methods/Nonylphenol.pdf

[121] Ferrara F, Fabietti F, Delise M and Funari E. Alkylphenols and alkiphenol ethoxylates contamination of crustaceans and fishes from the Adriatic Sea (Italy). Chemosphere 2005;59 (8), 1145-1150

[122] Shao B, Hu JY, Yang M, An W, and Tao S. Nonylphenol and Nonylphenol Ethoxylates in River Water, Drinking Water, and Fish Tissues in the Area of Chongqing, China. Archives of Environmental Contamination and Toxicology 2005; 48(4) 467-473.

[123] Basheer C, Lee HK, and Tan KS. Endocrine disrupting alkylphenols and bisphenol-A in coastal waters and supermarket seafood from Singapore. Baseline / Marine Pollution Bulletin 2004; 48 1145–1167.

[124] Lu YY, Chen ML, Sung FC, Wang PSG, and Mao IF. Daily intake of 4-nonylphenol in Taiwanese. Environment International 2007; 33(7) 903-910.

[125] Chang MH, Yan WL, Kao YM and Shih DYC. Studies on the Analysis of 4-Nonylphenol in Seafood. Annual Report of Food and Drug Research 2010; 1:87-98.

[126] Kannan K, Keith TL, Naylor CG, Staples CA, Snyder SA, and Giesy JP. Nonylphenol and nonylphenol ethoxylates in fish, sediment, and water from the Kalamazoo River, Michigan. Archives of Environmental Contamination and Toxicology 2003; 44(1):77-82.

[127] Guenther K, HeinkeV, Thiele B, Kleist E, Prast H and Raecker T. Endocrine Disrupting Nonylphenols are Ubiquitous in Food. Environmental Science and Technoloy 2002; 36:1676-1680.

[128] Thomson BM, Cressey PJ, Shaw IC. Dietary exposure to xenoestrogens in New Zealand. Journal of Enviromental Monitoring 2003;5:229-35.

[129] USFDA. CFR - Code of Federal Regulations Title 21. Sec. 175.105 Adhesives. [cited 26 March 2012]. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=175.105

ANNEX I

Lists of Potential Endocrine Disrupting Chemicals

Table 1: List of 66 Category 1 Substances with Concern by the European Commission Directorate-General for the Environment in 2000.

CASNR	Name	HPV/pers	Concern
12789-03-6	Chlordane	Highly Pers	High
57-74-9	Chlordane (cis- and trans-)	Highly Pers	High
143-50-0	Kepone = Chlordecone	Highly Pers	High
2385-85-5	Mirex	Highly Pers	High
8001-35-2	Toxaphene = Camphechlor	Highly Pers	High
50-29-3	DDT (technical) = clofenotane	HPV	High
50-29-3	p,p'-DDT = clofenotane	HPV	High
3563-45-9	Tetrachloro DDT = 1,1,1,2-Tetrachloro-2,2-bis(4-chlorophenyl)ethane	Highly Pers	High
50471-44-8	Vinclozolin	HPV	High
12427-38-2	Maneb	HPV	High
137-42-8	Metam Natrium	HPV	High
137-26-8	Thiram	HPV	High
12122-67-7	Zineb	HPV	High
58-89-9	Gamma-HCH = Lindane	HPV	High
330-55-2	Linuron (Lorox)	HPV	High
1912-24-9	Atrazine	HPV	High
34256-82-1	Acetochlor	HPV	High
15972-60-8	Alachlor	HPV	High
100-42-5	Styrene	HPV	High
118-74-1	Hexachlorobenzene = HCB	HPV	High
85-68-7	Butylbenzylphthalate (BBP)	HPV	High
117-81-7	Di-(2-ethylhexyl)phthalate (DEHP) = Dioctylphthalate (DOP)	HPV	High
84-74-2	Di-n-butylphthalate (DBP)	HPV	High
80-05-7	2,2-Bis(4-hydroxy-phenyl)propan = 4,4'-isopropylidenediphenol = Bisphenol A	HPV	High
1336-36-3	PCB	Pers.	High
35065-27-1	PCB153	Pers.	High
32774-16-6	PCB169	Pers.	High
2437-79-8	PCB47	Pers.	High
32598-13-3	PCB77	Pers.	High
53469-21-9	Aroclor 1242	Highly Pers	High
12672-29-6	Aroclor 1248	Pers.	High

CASNR	Name	HPV/pers	Concern
11097-69-1	Aroclor 1254	Highly Pers	High
11096-82-5	Aroclor 1260	Pers.	High
59536-65-1	PBBs = Brominated Biphenyls (mixed group of 209 Congeners)	Pers.	High
40321-76-4	1,2,3,7,8 Pentachlorodibenzo-dioxin	Pers.	High
No CAS 140	2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD)	Pers.	High
57117-31-4	2,3,4,7,8 Pentachlorodibenzofuran	Pers.	High
688-73-3	Tributyltin	Metal	High
No CAS 050	Tributyltin compounds	Metal	High
56-35-9	Tributyltin oxide = bis(tributyltin) oxide	HPV/ Metal	High
26354-18-7	2-propenoic acid, 2-methyl-, methyl ester = Stannane, tributylmeacrylate	Metal	High
No CAS100	Methoxyetylacrylate tinbutyltin, copolymer	Metal	High
4342-30-7	Phenol, 2-[[(tributylstannyl)oxy]carbony	Metal	High
4342-36-3	Stannane, (benzoyloxy)tributyl-	Metal	High
4782-29-0	Stannane, [1,2phenylenebis(carbonyl-oxy)	Metal	High
36631-23-9	Stannane, tributyl = Tributyltin naphtalate	Metal	High
85409-17-2	Stannane, tributyl-, mono(naphthenoyloxy	Metal	High
24124-25-2	Stannane, tributyl[(1-oxo-9,12-octa-decad	Metal	High
3090-35-5	Stannane, tributyl[(1-oxo-9-octa-decenyl)	Metal	High
26239-64-5	Stannane, tributyl[[[1,2,3,4,4a,4b,5,6,1	Metal	High
1983-10-4	Stannane, tributylfluoro-	Metal	High
2155-70-6	Tributyl[(2-methyl-1-oxo-2propenyl)-oxy]stannane	Metal	High
No CAS 099	Tributyltincarboxylate	Metal	High
26636-32-8	Tributyltinnaphthalate	Metal	High
No CAS 101	Tributyltinpoly-ethoxylate	Metal	High
2279-76-7	Tri-n-propyltin (TPrT)	Metal	High
No CAS 051	Triphenyltin	Metal	High
900-95-8	Fentin acetate	Metal	High
95-76-1	3,4-Dichloroaniline	HPV	High
108-46-3	Resorcinol	HPV	High
61-82-5	Amitrol = Aminotriazol	HPV	Medium
1836-75-5	Nitrofen	HPV	Medium
140-66-9	4-tert-Octylphenol=1,1,3,3-Tetramethyl4-butylphenol	HPV	Medium
25154-52-3	Phenol, nonyl-	HPV	Medium
1461-25-2	Tetrabutyltin (TTBT)	HPV/ Metal	Low
99-99-0	4-Nitrotoluene	HPV	Low

Table 2: Chemicals Suspected of Having Endocrine Disrupting Effects by the Ministry of the Environment, Government of Japan in 1998.

Substances	**Use**	**Restrictions**
1. Dioxins and furans	(Unintended product)	Air Pollution Law, Waste Disposal and Public Cleaning Law, POPs
2. Polychlorinated biphenyl (PCB)	Heat medium, non-carbon paper, electric product	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class I in 1974, stopped production in 1972, Water Pollution Control Law, Marine Pollution Prevention Law, Waste Disposal and Public Cleaning Law, Environmental Quality Standards for Groundwater, Soil Pollution, and Water Pollutants, POPs
3. Polybromobiphenyl (PBB)	Fire retardant	
4. Hexachlorobenzene (HCB)	Bactericide, organic synthetic raw material	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class I in 1979, unregistered in Japan, POPs
5. Pentachlorophenol (PCP)	Antiseptic, herbicide, bactericide	Lapsed in 1990, Water-pollutant Agricultural Chemicals, Poisonous and Deleterious Substances Control Law
6. 2,4,5-Trichlorophenoxy-acetic acid	Herbicide	Lapsed in 1975, Poisonous and Deleterious Substances Control Law, Food Sanitation Law
7. 2,4-Dichloro-phenoxyacetic acid	Herbicide	Registered
8. Amitrole	Herbicide, disperse dye, hardener for resins	Lapsed in 1975, Food Sanitation Law
9. Atrazine	Herbicide	Registered
10. Alachlor	Herbicide	Registered, Marine Pollution Prevention

Substances	Use	Restrictions
		Law
11. Simazine (CAT)	Herbicide	Registered, Water Pollution Control Law, Environmental Quality Standards for Groundwater, Soil Pollution, and Water Pollutants, Waste Disposal and Public Cleaning Law, Waterworks Law
12. Hexachlorocyclohexane, Ethyl parathion	Insecticide,	Hexachlorocyclohexane lapsed and banned sales in 1971, ethyl parathion lapsed in 1972
13. Carbaryl	Insecticide	Registered, Poisonous and Deleterious Substances Control Law, Food Sanitation Law
14. Chlordane	Insecticide	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class I in 1981, lapsed in 1968, Poisonous and Deleterious Substances Control Law, POPs
15. Oxychlordane	Chlordane metabolite	
16. trans-Nonachlor	Insecticide	Nonachlor unregistered in Japan, heptachlor lapsed in 1972
17. 1,2-dibromo-3-chloropropane	Insecticide	Lapsed in 1980
18. DDT	Insecticide	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class I in 1981, lapsed and banned sales in 1971, Food Sanitation Law, POPs
19. DDE and DDD	Insecticide (DDT metabolite)	Unregistered in Japan
20. Kelthane (Dicofol)	Acaricide	Registered, Food Sanitation Law
21. Aldrin	Insecticide	Law Concerning the Examination and

Substances	Use	Restrictions
		Regulation of Manufacture, etc., of Chemical Substances Class I in 1981, lapsed in 1975, Soil-persistent Agricultural Chemicals, Poisonous and Deleterious Substances Control Law, POPs
22. Endrin	Insecticide	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class I in 1981, lapsed in 1975, Crop-persistent Agricultural Chemicals, Poisonous and Deleterious Substances Control Law, Food Sanitation Law, POPs
23. Dieldrin	Insecticide	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class I in 1981, lapsed in 1975, Soil-persistent Agricultural Chemicals, Poisonous and Deleterious Substances Control Law, Food Sanitation Law, Harmful Substance Containing Household Products Control Law, POPs
24. Endosulfan (Benzoepin)	Insecticide	Poisonous and Deleterious Substances Control Law, Water-pollutant Agricultural Chemicals
25. Heptachlor	Insecticide	Law Concerning the Examination and Regulation of Manufacture,etc., of Chemical Substances Class I in 1986, lapsed in 1975, Poisonous and Deleterious Substances Control Law, , POPs
26. Heptachlor epoxide	Heptachlor metabolite	
27. Malathion	Insecticide	Registered, Food Sanitation Law
28. Methomyl	Insecticide	Registered, Poisonous and Deleterious Substances Control Law

Substances	Use	Restrictions
29. Methoxychlor	Insecticide	Lapsed in 1960
30. Mirex	Insecticide	Unregistered in Japan, POPs
31. Nitrofen	Herbicide	Lapsed in 1982
32. Toxaphene (Camphechlor)	Insecticide	Unregistered in Japan, POPs
33. Tributyltin	Antifouling paints on ships, antiseptic for fishnets	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substancesre TBTO: Class I, the remaining 13 substances: Class II TB in 1990, Harmful Substance Containing Household Products Control Law
34. Triphenyltin	Antifouling paints on ships, antiseptic for fishnets	Law Concerning the Examination and Regulation of Manufacture, etc., of Chemical Substances Class II in 1990, lapsed in 1990, Harmful Substance Containing Household Products Control Law
35. Trifluralin	Herbicide	Registered
36. Alkyl phenol (from C5 to C9) Nonyl phenol and Octyl phenol	Raw material for surface -active agents/ decomposition product	Marine Pollution Prevention Law
37. Bisphenol A	Raw material for resins	Food Sanitation Law
38. Di-(2-ethylhexyl)phthalate	Plasticiser for plastics	Monitoring substances in water environment
39. Butyl benzyl phthalate	Plasticiser for plastics	Marine Pollution Prevention Law
40. Di-n-butyl phthalate	Plasticiser for plastics	Marine Pollution Prevention Law
41. Dicyclohexyl phthalate	Plasticiser for	

Substances	Use	Restrictions
	plastics	
42. Diethyl phthalate	Plasticiser for plastics	Marine Pollution Prevention Law
43. Benzo(a)pyrene	(Unintended product)	
44. Dichlorophenol	Dye intermediate	Marine Pollution Prevention Law
45. Diethylhexyl adipate	Plasticiser for plastics	Marine Pollution Prevention Law
46. Benzophenone	Synthetic raw materials for medical products, perfume, etc.	
47. 4-Nitrotoluene	2,4-dinitro-toluene intermediate	Marine Pollution Prevention Law
48. Octachlorostyrene	(By-product of organic chlorine compound)	
49. Aldicarb	Insecticide	Unregistered in Japan
50. Benomyl	Bactericide	Registered
51. Kepone (Chlordecone)	Insecticide	Unregistered in Japan
52. Manzeb (Mancozeb)	Bactericide	Registered
53. Maneb	Bactericide	Registered
54. Metiram	Bactericide	Lapsed in 1975
55. Metribuzin	Herbicide	Registered, Food Sanitation Law
56. Cypermethrin	Insecticide	Registered, Poisonous and Deleterious Substances Control Law, Food Sanitation Law
57. Esfenvalerate	Insecticide	Registered, Poisonous and Deleterious

Substances	Use	Restrictions
		Substances Control Law
58. Fenvalerate	Insecticide	Registered, Poisonous and Deleterious Substances Control Law, Food Sanitation Law
59. Permethrin	Insecticide	Registered, Food Sanitation Law
60. Vinclozololin	Bactericide	Lapsed in 1998
61. Zineb	Bactericide	Registered
62. Ziram	Bactericide	Registered
63. Dipentyl phthalate		Not produced in Japan
64. Dihexyl phthalate		Not produced in Japan
65. Dipropyl phthalate		Not produced in Japan
66. Styrenes	Non-reacting substance of styrene-rubber plastic	
67. n-Butylbenzene	Synthesis intermediate, for liquid crystal manufacture	

NOTE

(1) Besides the above substances, cadmium, lead, and mercury are also suspected of having endocrine disrupting effects.

(2) The laws described in the restrictions column indicate that the substance is subject to restrictions under such laws.

(3) "Registered", "lapsed", "unregistered in Japan," "Soil-persistent Agricultural Chemicals," "Crop-persistent Agricultural Chemicals," "Water-pollutant Agricultural Chemicals" are based on the Agricultural Chemicals Regulation Law.

(4) POPs are residual organic pollutants specified in the "World Action Plan Concerning the Protection of the Marine Environment by Conducting Environmental Protection Activities on Land".

Table 3: Final List of Chemicals for Initial Tier 1 Screening 2009 by the U.S. Environmental Protection Agency.

Chemical Name	CAS Number	Pesticide Active Ingredient	HPV/Inert
2,4-D	94757	x	
4,7-Methano-1H-isoindole-1,3(2H)-dione,2-(2-ethylhexyl)-3a,4,7,7a-tetrahydro-	113484	x	
Abamectin	71751412	x	
Acephate	30560191	x	
Acetone	67641		x
Atrazine	1912249	x	
Benfluralin	1861401	x	
Bifenthrin	82657043	x	
Butyl benzyl phthalate	85687		x
Captan	133062	x	
Carbamothioic acid, dipropyl-, S-ethyl ester	759944	x	
Carbaryl	63252	x	
Carbofuran	1563662	x	
Chlorothalonil	1897456	x	
Chlorpyrifos	2921882	x	
Cyfluthrin	68359375	x	
Cypermethrin	52315078	x	
DCPA (or chlorthal-dimethyl)	1861321	x	
Diazinon	333415	x	
Dibutyl phthalate	84742		x
Dichlobenil	1194656	x	
Dicofol	115322	x	
Diethyl phthalate	84662		x
Dimethoate	60515	x	
Dimethyl phthalate	131113		x
Di-sec-octyl phthalate	117817		x

Chemical Name	CAS Number	Pesticide Active Ingredient	HPV/Inert
Disulfoton	298044	x	
Endosulfan	115297	x	
Esfenvalerate	66230044	x	
Ethoprop	13194484	x	
Fenbutatin oxide	13356086	x	
Flutolanil	66332965	x	
Folpet	133073	x	
Gardona (cis-isomer)	22248799	x	
Glyphosate	1071836	x	
Imidacloprid	138261413	x	
Iprodione	36734197	x	
Isophorone	78591		x
Linuron	330552	x	
Malathion	121755	x	
Metalaxyl	57837191	x	
Methamidophos	10265926	x	
Methidathion	950378	x	
Methomyl	16752775	x	
Methyl ethyl ketone	78933		x
Methyl parathion	298000	x	
Metolachlor	51218452	x	
Metribuzin	21087649	x	
Myclobutanil	88671890	x	
Norflurazon	27314132	x	
o-Phenylphenol	90437	x	
Oxamyl	23135220	x	
Permethrin	52645531	x	
Phosmet	732116	x	
Piperonyl butoxide	51036	x	
Propachlor	1918167	x	
Propargite	2312358	x	
Propiconazole	60207901	x	

Chemical Name	CAS Number	Pesticide Active Ingredient	HPV/Inert
Propyzamide	23950585	x	
Pyridine, 2-(1-methyl-2-(4-phenoxyphenoxy)ethoxy)-	95737681	x	
Quintozene	82688	x	
Resmethrin	10453868	x	
Simazine	122349	x	
Tebuconazole	107534963	x	
Toluene	108883		x
Triadimefon	43121433	x	
Trifluralin	1582098	x	

Table 4: Second List of Chemicals for Tier 1 Screening 2010 by the U.S. Environmental Protection Agency

Chemical Name	CAS Number	SDWA	PAI	RR Schedule
1,1,1,2-Tetrachloroethane	630-20-6	X		
1,1,1-Trichloroethane	71-55-6	X		
1,1,2-Trichloroethane	79-00-5	X		
1,1-Dichloroethane	75-34-3	X		
1,1-Dichloroethylene	75-35-4	X		
1,2,3-Trichloropropane	96-18-4	X		
1,2,4-Trichlorobenzene	120-82-1	X		
1,2-Dibromo-3-chloropropane (DBCP)	96-12-8	X		
1,2-Dichloroethane	107-06-2	X		
1,2-Dichloropropane	78-87-5	X		
1,3-Dinitrobenzene	99-65-0	X		
1,4-Dioxane	123-91-1	X		
1-Butanol	71-36-3	X		
2,4,5-TP (Silvex)	93-72-1	X		
2-Methoxyethanol	109-86-4	X		
2-Propen-1-ol	107-18-6	X		
4,4'-Methylenedianiline	101-77-9	X		
Acetaldehyde	75-07-0	X		
Acetamide	60-35-5	X		
Acetochlor	34256-82-1	X	X	
Acetochlor ethanesulfonic acid (ESA)	187022-11-3	X		
Acetochlor oxanilic acid (OA)	194992-44-4	X		
Acrolein	107-02-8	X	X	
Acrylamide	79-06-1	X		
Alachlor	15972-60-8	X	X	
Alachlor ethanesulfonic acid (ESA)	142363-53-9	X		
Alachlor oxanilic acid (OA)	171262-17-2	X		
alpha-Hexachlorocyclohexane	319-84-6	X		

Chemical Name	CAS Number	SDWA	PAI	RR Schedule
Aniline	62-53-3	X		
Bensulide	741-58-2	X	X	FY 2008
Benzene	71-43-2	X		
Benzo(a)pyrene (PAHs)	50-32-8	X		
Benzyl chloride	100-44-7	X		
Butylated hydroxyanisole	25013-16-5	X		
Carbon tetrachloride	56-23-5	X		
Chlordane	57-74-9	X		
Chlorobenzene	108-90-7	X		
cis-1,2-Dichloroethylene	156-59-2	X		
Clethodim	99129-21-2	X	X	FY 2008
Clofentezine	74115-24-5		X	FY 2007
Clomazone	81777-89-1		X	FY 2007
Coumaphos	56-72-4		X	FY 2008
Cumene hydroperoxide	80-15-9	X		
Cyanamide	420-04-2		X	FY 2008
Cyromazine	66215-27-8		X	FY 2007
Dalapon	75-99-0	X		
Denatonium saccharide	90823-38-4		X	FY 2008
Di(2-ethylhexyl) adipate	103-23-1	X		
Dichloromethane	75-09-2	X		
Dicrotophos	141-66-2	X	X	FY 2008
Dimethipin	55290-64-7	X	X	
Dinoseb	88-85-7	X		
Diuron	330-54-1	X	X	
Endothall	145-73-3	X	X	
Endrin	72-20-8	X		
Epichlorohydrin	106-89-8	X		
Erythromycin	114-07-8	X		
Ethylbenzene	100-41-4	X		
Ethylene dibromide	106-93-4	X		
Ethylene glycol	107-21-1	X		

Chemical Name	CAS Number	SDWA	PAI	RR Schedule
Ethylene thiourea	96-45-7	X		
Ethylurethane	51-79-6	X		
Etofenprox	80844-07-1		X	FY 2007
Fenamiphos	22224-92-6	X	X	FY 2008
Fenarimol	60168-88-9		X	FY 2007
Fenoxaprop-P-ethyl	71283-80-2		X	FY 2007
Fenoxycarb	72490-01-8		X	FY 2007
Flumetsulam	98967-40-9		X	FY 2008
Fomesafen sodium	108731-70-0		X	FY 2007
Fosetyl-Al (Aliette)	39148-24-8		X	FY 2008
Glufosinate ammonium	77182-82-2		X	FY 2008
HCFC-22	75-45-6	X		
Heptachlor	76-44-8	X		
Heptachlor epoxide	1024-57-3	X		
Hexachlorobenzene	118-74-1	X		
Hexachlorocyclopentadiene	77-47-4	X		
Hexane	110-54-3	X		
Hexythiazox	78587-05-0		X	FY 2007
Hydrazine	302-01-2	X		
Isoxaben	82558-50-7		X	FY 2008
Lactofen	77501-63-4		X	FY 2007
Lindane	58-89-9	X		
Methanol	67-56-1	X		
Methoxychlor	72-43-5	X		
Methyl tert-butyl ether	1634-04-4	X		
Metolachlor ethanesulfonic acid (ESA)	171118-09-5	X		
Metolachlor oxanilic acid (OA)	152019-73-3	X		
Molinate	2212-67-1	X	X	
Nitrobenzene	98-95-3	X		
Nitroglycerin	55-63-0	X		
N-Methyl-2-pyrrolidone	872-50-4	X		

Chemical Name	CAS Number	SDWA	PAI	RR Schedule
N-Nitrosodimethylamine (NDMA)	62-75-9	X		
n-Propylbenzene	103-65-1	X		
o-Dichlorobenzene	95-50-1	X		
o-Toluidine	95-53-4	X		
Oxirane, methyl-	75-56-9	X		
Oxydemeton-methyl	301-12-2	X	X	FY 2008
Oxyfluorfen	42874-03-3	X	X	
Paclobutrazol	76738-62-0		X	FY 2007
p-Dichlorobenzene	106-46-7	X	X	
Pentachlorophenol	87-86-5	X	X	
Perchlorate	14797-73-0	X		
Perfluorooctane sulfonic acid (PFOS)	1763-23-1	X		
Perfluorooctanoic acid (PFOA)	335-67-1	X		
Picloram	1918-02-1	X	X	
Polychlorinated biphenyls	1336-36-3	X		
Profenofos	41198-08-7	X	X	FY 2008
Propetamphos	31218-83-4		X	FY 2008
Propionic acid	79-09-4		X	FY 2008
Pyridate	55512-33-9		X	FY 2007
Quinclorac	84087-01-4		X	FY 2008
Quinoline	91-22-5	X		
Quizalofop-P-ethyl	100646-51-3		X	FY 2008
RDX	121-82-4	X		
sec-Butylbenzene	135-98-8	X		
Sodium tetrathiocarbonate	7345-69-9		X	FY 2008
Styrene	100-42-5	X		
Sulfosate	81591-81-3		X	FY 2007
Temephos	3383-96-8		X	FY 2008
Terbufos	13071-79-9	X	X	FY 2008
Terbufos sulfone	56070-16-7	X		
Tetrachloroethylene	127-18-4	X		
Thiophanate-methyl	23564-05-8	X	X	

Chemical Name	CAS Number	SDWA	PAI	RR Schedule
Toluene diisocyanate	26471-62-5	X		
Toxaphene	8001-35-2	X		
trans-1,2-Dichloroethylene	156-60-5	X		
Trichloroethylene	79-01-6	X		
Triethylamine	121-44-8	X		
Triflumizole	68694-11-1		X	FY 2007
Trinexapac-ethyl	95266-40-3		X	FY 2008
Triphenyltin hydroxide (TPTH)	76-87-9	X	X	
Vinclozolin	50471-44-8	X	X	
Xylenes (total)	1330-20-7	X	X	
Ziram	137-30-4	X	X	

CAS Number = Chemical Abstract Services Registry Number

SDWA = Drinking water chemical based on CCL 3 List or chemicals with National Primary Drinking Water Regulations

PAI = Pesticide active ingredient (Current pesticide registration exists)

RR = OPP Registration Review date

ANNEX II

Literature Search Strategy and Sources of Information

To identify literature relevant to the research questions, multiple database searches were conducted using internet search engines. Academic resources were obtained via google scholar, database of Wanfang, and databases available from the University of Hong Kong library (e.g., ProQuest, Pubmed, JSTOR and EBSCOhost databases). Searches for internet resources were conducted through the search engine Google.

The major search terms used will include but not limit to "endocrine disrupt*", "endocrine disrupt* AND dietary exposure, "environmental hormone AND food contact", "hormonally active AND food", etc. Publications related to occupational and environmental exposure will be excluded. All search terms were limited to publication dates ranging from 2002 (i.e. the year of the publication of the WHO study) to 2012 (inclusive) and with English or Chinese versions available.

In addition, references were also made to relevant publications from international and national authorities such as the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), the EC Directorate-General for the Environment (DG Environment), the U.S. Environmental Protection Agency (USEPA), European Food Safety Authorities (EFSA), the U.S. Food and Drug Administration (USFDA), the UK Food Standards Agency (UKFSA) and the Federal Institute for Risk Assessment (BfR) of Germany.

A summary of key terms by using databases of HKU libraries

Search terms					Publications retrieved
Endocrine disrupt*	AND	organochlorine pesticides	NOT		453
		organochlorine pesticides and dietary exposure			386
				occupation/ environment	94
		dioxin*			498
		dioxin* and dietary exposure			392
				occupation/ environment	81
		PCB*			504
		PCB* and dietary exposure			400
				occupation/ environment	44
		Styrene			400
		Styrene and dietary exposure			277
				occupation/ environment	97
		Bisphenol A			421
		Bisphenol A and dietary exposure			338
				occupation/ environment	179
		Phthalates			450
		Phthalates and dietary exposure			193
				occupation/ environment	43
		Organotins			422
		Organotins and dietary exposure			20
				occupation/ environment	10
		Nonylphenol			280
		Nonylphenol and dietary exposure			70
				occupation/ environment	5

*represents any groups of character, including no character.

ANNEX III

Abbreviations

2,3,4,7,8-PeCDF	2,3,4,7,8-pentachlorodibenzofuran
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
4-NP	4-nonylphenol
ADHD	Attention deficit hyperactivity disorder
AGI	Anogenital index
AR	Androgen receptor
BBP	Butylbenzylphthalate
BfR	Federal Institute for Risk Assessment of Germany
BPA	Bisphenol A
bw	Body weight
CFS	Centre for Food Safety
DBP	Di-butyl phthalate
DBT	Di-butyltin
DDT	Dichlorodiphenyl trichloroethane
DEHP	Di(2-ethylhexyl) phthalate
DG Environment	EC Directorate-General for the Environment
DIDP	Di-isodecyl phthalate
DINP	Di-isononyl phthalate
DMT	Dimethyltin
DOT	Di-n-octyltin
EC	European Commission
EDC	Endocrine disrupting chemicals
EFSA	European Food Safety Authority
EPS	Expanded polystyrene
ER	Estrogen receptor
EU	European Union
FAO	Food Agriculture Organization
HCB	Hexachlorobenzene
HPV	High production volume
IARC	International Agency for Research on Cancer
IPCS	International Programme for Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MMT	Monomethyltin
MOH	Ministry of Health

MOT	Mono-n-octyltin
MRLs	Maximum residue limits
NOAEL	No-observable-adverse-effect-level
NP	Nonylphenol
NPEs	Nonylphenol ethoxylates
NTP	National Toxicity Program
OECD	Organisation for Economic Co-operation and Development
PFCs	Perfluorocarbon compounds
PPARγ	Peroxisome proliferator-activated receptor gamma
PPARs	Peroxisome proliferator-activated receptors
POPs	Persistent organic pollutants
PC	Polycarbonate
PCBs	Polychlorinated biphenyls
PCB-126	3,3',4,4',5-pentachlorobiphenyl
PCDDs	Polychlorinated dibenzo-para-dioxins
PCDFs	Polychlorinated dibenzofurans
PMTDI	Provisional maximum tolerable daily intake
PS	Polystyrene
PTMI	Provisional tolerable monthly intake
PVC	Polyvinyl chloride
RASFF	Rapid Alert System for Food and Feed
RfD	Reference dose for chronic oral exposure
RXR	Retinoid X rceptors
SD	Styrene dimers
SM	Styrene monomer
SML	Specific migration limit
ST	Styrene trimers
TARL	Tolerable average residue level
TBT	Tributyltin
TBTH	Tributytin hydroxide
TDI	Tolerable daily intake
TDS	Total diet study
TEQ	Toxic equivalent
TPT	Triphenyltin
TPTH	Triphenyltin hydroxide
UKFSA	UK Food Safety Agency
USEPA	U.S. Environmental Protection Agency

USFDA	U.S. Food and Drug Administration
WHO	World Health Organization