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Joint FAO/WHO Expert Meeting to Review Toxicological and Health Aspects of Bisphenol A

Summary Report

including

Report of Stakeholder Meeting on Bisphenol A

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Ottawa, Canada

Note to readers

This summary report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the Food and Agriculture Organization of the United Nations and the World Health Organization.

A full, more detailed report, is in preparation and will be issued in due course.

The Joint FAO/WHO Expert Meeting to Review Toxicological and Health Aspects of Bisphenol A was supported by the European Food Safety Authority, Health Canada, the United States National Institute of Environmental Health Sciences and the United States Food and Drug Administration.

Table of contents

List of acronyms and abbreviations

AC_{50}	half-maximal activity concentration
BASC-2	Behavioural Assessment System for Children-2
BMD	benchmark dose
BMDL	95% lower limit on the benchmark dose
$BMDL_{10}$	95% lower limit on the benchmark dose for a 10% response
BMI	body mass index
BPA	bisphenol A
BRIEF-P	Behavior Rating Inventory of Executive Function (Preschool Version)
bw	body weight
CVD	cardiovascular disease
CYP	cytochrome P450
DES	diethylstilbestrol
DMBA	7,12-dimethylbenz[a]anthracene
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
ESR1	estrogen receptor 1
F_1	first filial generation
FAO	Food and Agriculture Organization of the United Nations
GD	gestation day
HPG	hypothalamic–pituitary–gonadal
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	lowest-observed-adverse-effect level
LOEC	lowest-observed-effect concentration
MS	mass spectrometry
MS/MS	tandem mass spectrometry
NHANES	National Health and Nutrition Examination Survey (USA)
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (USA)
P_0	first parental generation
PBPK	physiologically based pharmacokinetic
PC	polycarbonate
PND	postnatal day
PVC	polyvinyl chloride
USA	United States of America
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
WHO	World Health Organization

Executive summary

Bisphenol A (BPA) is an industrial chemical that is widely used in the production of polycarbonate (PC) plastics (used in food contact materials, such as baby bottles and food containers) and epoxy resins (used as protective linings for canned foods and beverages and as a coating on metal lids for glass jars and bottles). These uses result in consumer exposure to BPA via the diet.

Although a large number of studies on the toxicity and hormonal activity of BPA in laboratory animals have been published, there have been considerable discrepancies in outcome among these studies with respect to both the nature of the effects observed as well as the levels at which they occur. This has led to controversy within the scientific community about the safety of BPA, as well as considerable media attention.

In light of uncertainties about the possibility of adverse human health effects at low doses of BPA, especially on reproduction, the nervous system and behavioural development, and considering the relatively higher exposure of very young children compared with adults, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) jointly organized an Expert Meeting to assess the safety of BPA.

Analytical methods for the determination of BPA in food and biological samples

Sensitive and reliable analytical methods are available for the determination of BPA in both food and biological samples. Solvent extraction and solid-phase extraction are the most commonly used and most effective methods for the extraction of BPA in food and biological samples. Although isotope dilution methods based on mass spectrometry and tandem mass spectrometry are the most reliable for the detection of BPA, many of the results of BPA determination in both food and biological samples have been generated by methods that are not based on mass spectrometry.

The majority of methods used to measure free and total BPA in food and biological samples have been validated for certain performance parameters, such as accuracy, precision, recovery and limit of detection. Most methods fulfil the requirements of single-laboratory validation. For biological samples, however, validation of methods for conjugated BPA is very limited. By the current standards of analytical science, findings of BPA in food samples and most biological samples are reliable. Nevertheless, care needs to be taken to avoid cross-contamination with trace levels of BPA during sample collection, storage and analysis.

Occurrence of BPA in food

The Expert Meeting considered BPA concentrations in food from food surveys and from migration studies from food contact materials. Free BPA levels were no more than 11 μg/l in canned liquid infant formula as consumed and no more than 1 μg/l in powdered infant formula as consumed. In toddler food, BPA concentrations were approximately 1 μg/kg on average. Total BPA levels were below 8 μg/l in breast milk. For adult foods, 30 studies representing about 1000 samples from several countries were available, and the data were segregated according to food type. The occurrence data that were deemed to be valid for use in the exposure assessment were tabulated. For adult foods, average concentrations ranged from 10 to 70 μg/kg in solid canned food and from 1 to 23 μg/l in liquid canned food. For the

migration of BPA from PC, worst-case realistic uses were defined, and a maximum migration of 15 μg/l was selected for use in the exposure assessment.

Exposure assessment

The Expert Meeting estimated exposure to BPA by reviewing published exposure estimates in seven countries and regions and by calculating international exposure from the available information on food consumption patterns and the occurrence of BPA in foods relevant to the population groups of interest.

On the basis of the most relevant national published estimates, the exposure of adults to BPA was <0.01–0.40 μg/kg body weight (bw) per day at the mean and 0.06–1.5 μg/kg bw per day at the 95th/97.5th percentile. For young children and teenagers, mean exposure was 0.1–0.5 μg/kg bw per day, and exposure at the 95th/97.5th percentile was 0.3–1.1 μg/kg bw per day.

To estimate international exposure to BPA, the Expert Meeting considered a variety of possible scenarios of model diets, combining daily 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 (average and maximum concentrations).

The mean exposure of exclusively breastfed babies (0–6 months) to BPA is estimated to be 0.3 μg/kg bw per day, and exposure at the 95th percentile is estimated to be 1.3 μg/kg bw per day. Once solid foods are introduced (at 6–36 months), exposure to BPA decreases relative to body weight. Exposure estimates are generally higher for infants fed with liquid compared with powdered formula and for infants fed using PC compared with non-PC bottles. The highest estimated exposure occurs in infants 0–6 months of age who are fed with liquid formula out of PC bottles: 2.4 μg/kg bw per day at the mean and 4.5 μg/kg bw per day at the 95th percentile. For children older than 3 years, highest exposure estimates did not exceed 0.7 μg/kg bw per day at the mean and 1.9 μg/kg bw per day at the 95th percentile. For adults, highest exposure estimates did not exceed 1.4 μg/kg bw per day at the mean and 4.2 μg/kg bw per day at the 95th percentile.

Based on the limited data available, exposure to BPA from non-food sources is generally lower than that from food by at least an order of magnitude for most population subgroups.

Metabolism and toxicokinetics

The toxicokinetics of orally administered BPA has been studied in rodents, non-human primates and humans. BPA is extensively absorbed from the gastrointestinal tract, undergoing substantial presystemic Phase II metabolism in the gut and liver, primarily to the glucuronide conjugate. Conversion to the glucuronide conjugate is critical because, unlike the aglycone (i.e. free or unconjugated) form of BPA, it does not bind to the estrogen receptor. In rodents, BPA glucuronide is subjected to biliary excretion, enterohepatic recirculation and principally faecal excretion; non-human primates and humans quantitatively excrete conjugated forms of BPA in urine within 6 h, consistent with its short half-life. Aglycone BPA does not accumulate in the body.

Despite some differences in BPA metabolism and disposition between adult rodents and primates, internal exposures to aglycone BPA are remarkably similar. This apparent lack of requirement for allometric scaling suggests that a specific adjustment for interspecies differences in toxicokinetics is not required for adults.

Lactational transfer in rats appears to be limited, and placental transfer occurs almost exclusively for the aglycone form of BPA.

The extensive data from fetal, neonatal and adult experimental animals in conjunction with human pharmacokinetic and biomonitoring data have prompted the development of several physiologically based pharmacokinetic (PBPK) models. These models have estimated circulating concentrations of aglycone BPA in the picomole per litre range for children and adults with no identified sources of exposure.

Biological activities of BPA

Many of the physiological effects of BPA have been described in the context of its ability to interact with classic estrogen receptors. BPA can have estrogenic activity, but it should not be considered to act only as an estrogen or even a selective estrogen receptor modulator. The available data show that BPA's biochemical and molecular interactions are complex, involving classic estrogen receptors as well as a variety of other receptor systems and molecular targets. The complexity of BPA's interactions and concentration ranges at which the observations have been made make it challenging to conclude whether a given in vivo finding is biologically plausible based on consistency and potency of a response compared with estrogens alone.

Biomonitoring data

Urinary concentrations of total (free plus conjugated) BPA, particularly in spot samples, have often been used to evaluate exposure to BPA from all sources. Available data from biomonitoring studies in North America, Europe and South-east Asia suggest that human exposure to BPA is widespread across the lifespan in these parts of the world. To obtain biomonitoring-based exposure estimates, the total BPA urinary concentrations were multiplied by the age-specific estimated 24 h urinary output volume (presumed to be equivalent to the daily exposure) and divided by body weight. Using these assumptions, biomonitoring-based median exposure estimates are in the range of 0.01–0.05 μg/kg bw per day for adults and somewhat higher (0.02–0.12 μg/kg bw per day) for children. The 95th percentile exposure estimates are 0.27 μg/kg bw per day for the general population and higher for infants (0.45–1.61 μg/kg bw per day) and children 3–5 years of age (0.78 μg/kg bw per day). These estimates are comparable to those based on concentrations in food and amounts of food consumed.

BPA has a relatively short elimination half-life (<2 h for urinary excretion). BPA concentrations in blood decrease quickly after exposure and are considerably lower than those in urine. Published measured plasma levels are hard to interpret, as it is difficult to rule out cross-contamination. Therefore, concentrations of BPA in blood have limited value for epidemiological studies at present, but efforts are under way to improve measurements of BPA in blood.

Epidemiological studies

There are a limited number of epidemiological studies, with the majority using cross-sectional designs and a single measure of urinary BPA. Cross-sectional studies concurrently assess BPA exposure and health outcomes, thus limiting their interpretability, especially for outcomes that have long latency periods (e.g. cardiovascular disease [CVD], diabetes). Given the short half-life of BPA, the use of a single urine sample to categorize exposure is another limitation of most of the human studies described below:

- Three epidemiological studies investigated the association of urinary BPA concentrations with semen quality. Although all three studies reported associations of increased urinary BPA concentration with one or more measures of reduced semen quality, the association in two of the studies was not statistically significant. Other limitations include their cross-sectional designs and incomplete assessment of occupational co-exposure in one of the three studies.
- The evidence for an association of BPA with altered age of pubertal onset in girls in two epidemiological studies was limited and inconsistent.
- It is difficult to draw any conclusions from two published epidemiological studies that have examined the association of BPA with perinatal outcomes and body mass index (BMI), but one prospective cohort study that examined the relationship of serial BPA urinary concentrations in pregnant women with neurobehavioural outcomes suggests that prenatal BPA exposures—especially those during early pregnancy—are associated with the later development of externalizing behaviours, such as aggression and hyperactivity, particularly in female children. Replication of this study using large prospective birth cohorts with serial measures of urinary BPA during pregnancy is a high-priority research need.
- Two cross-sectional analyses of data from the United States National Health and Nutrition Examination Survey (NHANES) reported associations of BPA exposure with self-reported diagnosis of pre-existing CVD and diabetes. These cross-sectional analyses, although garnering scientific and public attention, have several important weaknesses that limit their interpretation.

Acute and repeated-dose toxicity

BPA is of low acute toxicity. Repeated-dose studies in rats and mice have shown effects on the liver, kidney and body weight, with a lowest no-observed-adverse-effect level (NOAEL) of 5 mg/kg bw per day. There are no specific long-term toxicity studies with BPA other than those conducted to examine its carcinogenicity.

Genotoxicity

BPA is not a mutagen in in vitro test systems, nor does it induce cell transformation. BPA has been shown to affect chromosomal structure in dividing cells in in vitro studies, but evidence for this effect in in vivo studies is inconsistent and inconclusive. BPA is not likely to pose a genotoxic hazard to humans.

Carcinogenicity

BPA has been studied in rodent carcinogenicity studies with dosing beginning in young adulthood. The studies, although suggestive of increases in certain tumour types, were considered not to provide convincing evidence of carcinogenicity. BPA exposure during the perinatal period has been reported to alter both prostate and mammary gland development in ways that may render these organs more susceptible to the development of neoplasia or preneoplastic conditions with subsequent exposures to strong tumour initiating or promoting regimens. In the absence of additional studies addressing identified deficiencies, there is currently insufficient evidence on which to judge the carcinogenic potential of BPA.

Reproductive and developmental toxicity of BPA in mammalian species

Over the last several decades, there have been hundreds of experimental studies on the potential reproductive and developmental toxicity of BPA in laboratory and domestic animal species, the large majority of the studies being conducted with rats and mice. These studies have been reviewed recently by several regulatory bodies, and most have identified an oral

reproductive and developmental NOAEL of 50 mg/kg bw per day. In spite of these reviews and the large number of animal studies, there remains considerable debate about the potential for low-dose effects of BPA in humans. The Expert Meeting considered the "new" studies since 2008 and a recent draft review of BPA and integrated these with the existing data to provide an overall summary of the potential low-dose effects (below 1 mg/kg bw per day) of BPA that may be relevant to human health.

Where the only evidence for adverse reproductive and developmental effects of oral BPA comes from studies in rats or mice with no relevant evidence from humans, non-human primates or domestic animals, account needs to be taken of key species differences that may limit straightforward translation of findings from rodents to humans.

The Expert Meeting concluded that there is considerable uncertainty as to whether BPA has any effect in rodents on conventional reproductive or developmental endpoints at doses below 1 mg/kg bw per day by the oral or subcutaneous route or potential effects in humans at current exposure levels.

Neurobehavioural, neurotoxic and neuroendocrine effects

Developmental exposure to BPA does not appear to affect sensory systems, spontaneous activity or female sexual behaviour in laboratory animals. Changes in brain biochemical signalling, morphometric and cellular end-points within sexually dimorphic anatomical structures and neuroendocrine end-points were reported at dietary exposures below 5 mg/kg bw per day. Importantly, methodological limitations introduce uncertainty in interpretation of the findings. Based on the available data, changes in anxiety and convergence of anatomical brain sex differences were identified as end-points suggestive of effects with potential human relevance, but where further investigation is necessary to address uncertainty.

Immunotoxicity

The Expert Meeting concurs with previous reviews that BPA is capable of producing a skin sensitization response in humans. There is no clear evidence that BPA interferes with immune function.

Cardiovascular effects

The toxicological data do not indicate a clear effect of BPA on cardiovascular function. The Expert Meeting is aware of ongoing studies on cardiovascular function that will inform conclusions regarding cardiac end-points in the near future.

Metabolic disorders

Metabolic disorders are an emerging area of research, and the currently available data are not sufficient to allow any conclusions to be reached regarding potential risk for humans. However, the available data suggest that further assessment of the potential effects of BPA on adiposity, glucose or insulin regulation, lipids and other end-points related to diabetes or metabolic syndrome is warranted. The Expert Meeting was aware that some studies are already ongoing to address some of these issues.

Hazard characterization

Establishing a "safe" exposure level for BPA continues to be hampered by a lack of data from experimental animal studies that are suitable for risk assessment. Many research studies have design and analysis issues that limit their utility for this purpose. Controversy continues over the biological significance of many of the more sensitive end-points and whether studies that

have assessed only conventional end-points are adequate for detection of all potentially relevant effects. Continued research into the toxicokinetics of BPA and its estrogenic and other mechanisms of action will be needed before it is possible to determine the appropriate points of departure (e.g. NOAEL, LOAEL, benchmark dose) for human risk assessment with confidence.

In summary, the Expert Meeting concluded that:

- For many end-points, points of departure are much higher than human exposure. Hence, there is no health concern for these end-points.
- Studies on developmental and reproductive toxicity in which conventional end-points were evaluated have shown effects only at high doses, if at all.
- However, some emerging new end-points (sex-specific neurodevelopment, anxiety, preneoplastic changes in mammary glands and prostate in rats, impaired sperm parameters) in a few studies show associations at lower levels.
    - The points of departure for these low-dose effects are close to the estimated human exposure, so there would be potential for concern if their toxicological significance were to be confirmed.
    - However, it is difficult to interpret these findings, taking into account all available kinetic data and current understanding of classical estrogenic activity. However, new studies indicate that BPA may also act through other mechanisms.
    - There is considerable uncertainty regarding the validity and relevance of these observations. While it would be premature to conclude that these evaluations provide a realistic estimate of the human health risk, given the uncertainties, these findings should drive the direction of future research with the objective of reducing this uncertainty.

Alternative materials

Some alternatives to BPA-containing materials for PC bottles and containers and epoxy can linings are available on the market or proposed for use. As a result of the broad usage of BPA, it appears that it will not be possible to identify a single replacement for all uses, particularly for can coatings. The functionality and safety of any replacement material need to be carefully assessed.

Recommendations

The Expert Meeting identified a number of gaps in knowledge and provided a range of recommendations for the generation of further information and the design of new studies to better understand the risk to human health posed by BPA.

Introduction

Bisphenol A (BPA) is a high-production-volume industrial chemical that is widely used in the production of polycarbonate (PC) plastics and epoxy resins, as well as other applications. PC is widely used in food contact materials, such as infant feeding bottles, microwave ovenware, food containers and water bottles. Epoxy resins are used as protective linings for a variety of canned foods and beverages and as a coating on metal lids for glass jars and bottles, including containers used for infant formula. These uses result in the exposure of consumers, including infants, to BPA through the diet. Other sources of human exposure have also been proposed.

A very large number of studies on the toxicity and hormonal activity of BPA in laboratory animals have been published. There have been considerable discrepancies in outcome among these studies with respect to both the nature of the effects observed as well as the levels at which they occur. In particular, the effects in some of the research studies were described at dose levels several orders of magnitude below those at which effects were reported in studies conducted in accordance with standard test guidelines. This has led to controversy within the scientific community about the safety of BPA and has resulted in various national authorities taking different risk management actions. The issue has also received much attention in the media, which has led to a concerned general public.

In light of the uncertainties about the possibility of adverse human health effects at low doses of BPA, especially on reproduction, the nervous system and behavioural development, and considering the relatively higher exposure of very young children compared with adults, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) jointly organized an ad hoc Expert Meeting to assess the safety of BPA. The meeting was supported by the European Food Safety Authority, Health Canada, the National Institute of Environmental Health Sciences of the United States of America (USA) and the United States Food and Drug Administration.

An open call for experts was published in November 2009 with a March 2010 deadline, and 90 applications were received. The experts invited to participate in the Expert Meeting were selected by FAO and WHO according to expertise needed and taking regional and gender aspects into account. Drafters for preparation of the background papers in advance of the meeting were identified from the qualified experts. A list of participants is included as Annex 1. Dr Lynn Goldman, George Washington University, served as Chairperson, Dr Antonia Calafat, United States Centers for Disease Control and Prevention, served as Vice-Chairperson, and Dr Alan Boobis, Imperial College London, and Dr Eddo Hoekstra, Joint Research Centre of the European Commission, served as Co-Rapporteurs. The meeting was held in Ottawa, Canada, on 2–5 November 2010. The agenda as adopted is included as Annex 2.

In addition to the Expert Meeting, FAO and WHO felt it was important to provide an opportunity for stakeholders to present their views on the current project to review toxicological and health aspects of BPA. FAO and WHO therefore held a stakeholder meeting on 1 November 2010 with all persons or organizations who had submitted a written request to participate in response to the public announcement of the meeting. The experts

invited for the Expert Meeting also participated in the stakeholder meeting. The participating stakeholders and the key concerns raised at the stakeholder meeting are included in Annex 3.

The Expert Meeting was opened by Dr Annika Wennberg, FAO Joint Secretary to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), who welcomed the meeting participants and expressed her hopes for a productive meeting. She outlined the scope, focus and conduct of the meeting, emphasizing that its focus was on all aspects of human health risk assessment, but that risk management was excluded from the scope of the meeting. Dr Angelika Tritscher, WHO Joint Secretary to JECFA, expressed her appreciation for the tremendous amount of effort that had already been put into this project and thanked the European Food Safety Authority, Health Canada, the United States National Institute of Environmental Health Sciences and the United States Food and Drug Administration for their support of the meeting.

The goal of the Expert Meeting was to analyse all available scientific data in order to evaluate the potential impact of BPA exposure on human health, with a focus on dietary exposure to low doses of BPA. Other relevant sources of exposure were also to be considered. Previous work and risk assessments carried out at national and international levels were to form part of the information to be assessed. The main topics to be assessed included:

- chemistry and analytical methods;
- occurrence of BPA in food, including possible migration from food contact materials;
- exposure to BPA from different sources, including specifically exposure through food as a result of migration from food contact materials;
- biochemistry and toxicity of BPA;
- review of epidemiological studies (human data);
- dose–response assessment;
- human health risk characterization, including consideration of sensitive subpopulations and sensitive life stages; and
- consideration of alternatives to BPA.

The Expert Meeting was also to identify uncertainties and knowledge gaps to guide future research efforts. The information and views presented at the stakeholder meeting (Annex 3) were to be considered by the Expert Meeting to the extent possible.

Declarations of interests

FAO and WHO informed the group that all experts had completed declaration of interest forms. Declared interests had been evaluated, and no conflicts related to BPA had been identified. One expert had received a research grant for tobacco research through a foundation that receives money from the tobacco industry, and, in line with WHO's strong position on tobacco research, the expert was excluded from the meeting.

Declared interests and potential conflicts were discussed at the beginning of the meeting.

The following experts have taken a position on BPA, mostly in the line of their regular duties or as participants in expert panels: Jason Aungst, Allan Bailey, Scott Belcher, John Bucher, Antonia Calafat, Anna Federica Castoldi, Mark Feeley, Lynn Goldman, Earl Gray, Ursula Gundert-Remy, Helen Håkansson, Kenneth Portier, Richard Sharpe, Kristina Ann Thayer, Michelle Twaroski and Frederick vom Saal.

The following experts have received research grants specific for BPA from public sources: Scott Belcher, Helen Håkansson, Russ Hauser, Vasantha Padmanabhan, Heather Patisaul and Frederick vom Saal.

The following experts have declared interests:

- Alan Boobis has consulted for chemical manufacturers on substances unrelated to BPA. To our knowledge, these manufacturers do not produce BPA. He is a (non-remunerated) member of the board of trustees of a research organization, active in the field of human health, toxicology, risk assessment and the environment, that draws its membership from the chemical, agrochemical, petrochemical, pharmaceutical, biotechnology and consumer products industries.
- Frederick vom Saal has provided consultations for a stainless steel water bottle manufacturer in a litigation in which he defended the position that BPA has endocrine disrupting activity. He has also received a retainer for future consulting from a law firm involved in a class action suit regarding the labelling of products containing BPA in which he would be required to provide evidence of adverse health effects of BPA. The tribunal has, however, not yet allowed the suit to proceed. He received research support to evaluate the effects of BPA from foundations receiving funds from corporate and private organizations that do not directly or indirectly produce BPA.

It was concluded that these interests do not warrant exclusion from the discussions of the meeting.

Summary, conclusions and recommendations

1. Analytical methods for the determination of BPA in food and biological samples

Sensitive and reliable analytical methods are available for the determination of BPA in both food and biological samples. Solvent extraction and solid-phase extraction are the most commonly used and most effective methods for the extraction of BPA in food and biological samples. Although isotope dilution methods based on mass spectrometry (MS) and tandem mass spectrometry (MS/MS) are the most reliable for the detection of BPA, many of the results of BPA determination in both food and biological samples have been generated by non-MS-based methods.

The majority of methods used to measure free and total BPA in food and biological samples have been validated for certain performance parameters, such as accuracy, precision, recovery and limit of detection. Most methods fulfil the requirements of single-laboratory validation. For biological samples, however, validation of methods for conjugated BPA is very limited; only one study validated its method for conjugated BPA for some parameters. Proficiency testing programmes for measuring BPA are available, and some laboratories have participated regularly or occasionally, but validation of methods for BPA through interlaboratory collaborative studies has not yet been conducted. It is difficult to rule out cross-contamination with trace levels of free BPA during sample collection, storage and analysis because of the ubiquitous presence of BPA in the environment.

The Expert Meeting recommends that:

- Analytical methods should be validated according to published guidelines for single-laboratory validation, such as the International Union of Pure and Applied Chemistry (IUPAC) guidelines, to include at least the following method performance parameters: limit of detection, limit of quantification, repeatability, recovery, linearity and range of calibration curve.
- MS- or MS/MS-based isotope dilution methods should be used for the determination of BPA whenever possible. Results from non-MS-based methods should be confirmed by MS methods, especially for food and biological samples.
- The enzyme-linked immunosorbent assay (ELISA) could be used for screening purposes, but it is not adequate for the quantitative determination of BPA in food and biological samples.
- Efforts should be made to produce commercially available, high-purity conjugated BPA standards for method validation purposes for biological samples.
- Efforts should be made to avoid cross-contamination during sample preparation and analysis, particularly when measuring unconjugated BPA concentrations, and method blanks and certified reference materials (if available) should be included in the analysis.
- Laboratories are encouraged to participate in current proficiency testing programmes to assess the reliability of the data they are producing.
- Interlaboratory studies should be conducted to validate methods for different types of food and biological samples.

2. Sources and occurrence of BPA

BPA is a monomer used primarily in the production of PC plastics and epoxy resins. Over 95% of the world consumption of BPA in 2009 was for these two purposes.

PC applications include large returnable, refillable water bottles and food service items such as sports bottles, baby bottles, pitchers, tumblers, home food containers and flatware. Epoxy applications include protective coatings for the interiors and exteriors of food and beverage containers as well as dental materials. BPA derivatives are used, to a limited extent, as additives for polyvinyl chloride (PVC). BPA is also present in recycled and thermal paper.

The Expert Meeting considered BPA concentrations in food from food surveys and BPA migration from food contact and dental materials. BPA concentrations in air, dust and water were also considered.

The Expert Meeting noted that by far the majority of studies on BPA concentrations reported from food surveys were from food and beverages in epoxy-coated cans and, to a minor extent, glass containers with coated metal lids. Similarly, the majority of studies on BPA concentrations in food as a result of migration from food contact materials involved PC infant feeding bottles. A few studies on BPA concentrations in paper were available.

BPA concentrations in food from food survey data were broken down by food type and age: infant formula and breast milk (0–6 months), baby and toddler food (6–12 months) and adult food. Most available data are for free (aglycone) BPA. However, in some cases (e.g. for breast milk), one would like to use total concentrations of BPA (i.e. free plus conjugated BPA) for exposure assessment.

For breast milk, three studies representing more than 200 samples generally gave total BPA levels below 8 µg/l; however, two of the studies were considered to be of questionable utility because of their analytical shortcomings.

For canned liquid infant formula, six studies representing more than 50 samples gave free BPA levels below 10 µg/l as consumed. The studies are primarily from North America. One of the studies was considered to be questionable in terms of method validation.

For toddler food, one study in North America, representing about 100 samples, gave free BPA levels of about 1 µg/kg at the mean. Another study found no detectable BPA, but the limit of detection of the method used was relatively high.

For adult foods, 30 studies representing about 1000 samples from several countries were available. The data were segregated according to food type. Levels in beverages were lower than levels in foods, levels in fruits were lower than levels in vegetables, and levels in fatty foods were higher than levels in all other foods. The data on canned foods were considered to be sufficient for exposure assessment.

For food contact materials, numerous studies (primarily on bottles) examined various food simulants, contact times, bottle handling practices (washing, detergents, etc.) and bottle age. BPA levels were generally higher for non-aqueous simulants, higher temperatures, higher contact times and increasing pH of the contact medium. The data on PC articles were considered to be adequate.

For the migration of BPA from PC, worst-case realistic uses were defined. For the use of baby bottles, the worst-case scenario was defined as filling the bottle with boiling water, adding milk formula and leaving the bottle to cool down. In the case of PC tableware, the worst-case scenario was represented by a 30 min contact time at 95 °C. Because of the large distribution of available test results, a maximum migration was selected for both situations for use in the exposure assessment.

Several data exist on the levels of BPA in tap water and bottled water. Because the concentrations vary widely, a maximum concentration of BPA in water was selected for use in the exposure assessment.

The concentrations of BPA in air and dust are widely distributed, and two papers show that there is no difference between concentrations of BPA in indoor and outdoor air. Published estimates of exposure to BPA from air and dust were used in the exposure assessment (see section 3.3).

Few studies on BPA in paper packaging, paper treatment water and thermal paper were available. BPA levels were higher in recycled paper than in virgin paper. Additional studies on BPA migration from paper packaging to food are needed.

BPA levels in saliva from dental materials were low. The Expert Meeting determined that there was no need to collect additional data on BPA levels from dental materials, as exposure is short term and unlikely to contribute substantially to chronic exposure.

Table 1 summarizes the occurrence data that were deemed to be valid for use in the exposure assessment.

The following data gaps were identified by the Expert Meeting:

- Further surveys of BPA levels in breast milk from countries other than the USA are needed. Such studies should employ analytical methods that determine both free and total BPA.
- Further surveys of BPA concentrations in infant formula from countries outside of North America are needed.
- Further surveys of BPA levels in toddler food from countries outside of North America, especially if such food is packed in metal cans, are needed.
- Additional studies on BPA migration from paper packaging to food are needed.

3. Exposure assessment

The Expert Meeting estimated exposure to BPA by reviewing published exposure estimates from seven countries and regions and by calculating international exposure from the available information on food consumption patterns and the occurrence of BPA in foods relevant to the population groups of interest. Non-dietary sources of exposure were also considered.

3.1 National estimates of exposure

The methodologies used and the population groups reported on in the published literature vary considerably. Depending on a range of assumptions about BPA concentrations in foods,

Table 1. Occurrence data for BPA in food and beverages

Matrix / Reference	Concentration (µg/l or µg/kg)		Number of samples
	Average	Maximum	
Human breast milk (Ye et al., 2006)	1.9	7.3	20
Liquid milk formula, ready to feed[a]			
Cao et al. (2008)	5.1	10.2	3
Ackerman et al. (2010)	5.05	10	39
Goodson, Summerfield & Cooper (2002)	<2	<2	4
Overall	4	10	46
Liquid milk formula, concentrate[a]			
Ackerman et al. (2010)	5.71	11	38
Biles, McNeal & Begley (1997)	2.6	6.1	14
EWG (2007)	1.2	8.5	6
Cao et al. (2008)	2.6	5.1	18
Overall	3.0	11	74
Liquid milk formula, overall[a]	3.5	11	120
Powdered milk formula[a] (Ackerman et al., 2010)	0.09	0.4	26
Infant food, glass jars (Cao et al., 2009)			
Desserts	0.38	0.83	9
Fruits	0.6	3.7	26
Meats	1.1	7.2	25
Vegetables	1.2	7.2	39
Overall	0.82	7.2	99
Canned food, solid[b]			
Fruits	9.8		70
Vegetables	32.4		305
Grains	42.7		22
Meat (no soups or seafood)	69.6		70
Soups	49.1		66
Seafood	26.6		166
Desserts	26.7		11
Overall	36.7		710
Canned food, liquid[b]			
Drinks, carbonated (cola, beer, soda, tonic)	1.0		128
Drinks, non-carbonated (tea, coffee, other)	23.2		131
Migration from PC			
Baby bottles (Maragou et al., 2008)		15	6
Tableware (Kawamura et al., 1998)		2	3
Tap water and bottled water		1	>100

[a] Expressed as consumed.

[b] Brotons et al. (1995); Horie et al. (1999); Kawamura, Sano & Yamada (1999); Imanaka et al. (2001); Yoshida et al. (2001); Goodson, Summerfield & Cooper (2002); Kataoka, Ise & Narimatsu (2002); Kang & Kondo (2003); Braunrath et al. (2005); Munguia-Lopez et al. (2005); Thomson & Grounds (2005); Maragou et al. (2006); Sun et al. (2006); EWG (2007); Podlipna & Cichna-Markl (2007); Poustka et al. (2007); Sajiki et al. (2007); Shao et al. (2007); Garcia-Prieto et al. (2008); Grumetto et al. (2008); Yonekubo, Hayakawa & Sajiki (2008); Bendito et al. (2009); Cao, Corriveau & Popovic (2009, 2010a,b); Consumers Union (2009); Rastkari et al. (2010); Vinas et al. (2010).

consumption amounts and frequency of consumption of foods containing BPA, exposure to BPA reported in the literature and in different countries can be substantially overestimated in some population groups, in particular infants. However, these studies were considered by the Expert Meeting.

The Expert Meeting concluded that on the basis of the most relevant national published estimates, the mean exposure of adults to BPA was <0.01–0.40 μg/kg body weight (bw) per day, and exposure at the 95th/97.5th percentile was 0.06–1.5 μg/kg bw per day. For young children and teenagers, mean exposure was 0.1–0.5 μg/kg bw per day, and exposure at the 95th/97.5th percentile was 0.3–1.1 μg/kg bw per day.

3.2 International estimates of exposure

To estimate international exposure to BPA, the Expert Meeting 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 (average and maximum concentrations from Table 1 above). Consequently, a number of exposure estimates were derived.

Owing to the lack of individual food consumption data available for any age group other than infants 0–6 months of age, the budget method model was used. This model is considered to be highly protective of consumers, as it is based on the maximum physiological levels of daily consumption, which are 0.05 kg/kg bw for solid food and 0.1 ml/kg bw for liquid food. In order to account for the type of solid food introduced during the diversification step (packaged or unpackaged), three different scenarios were used, assuming that 100%, 50% or 25% of the food consumed was packaged in articles manufactured with BPA.

Except for breast milk, all concentration data used in the calculations were expressed as free BPA. All estimates were made for mean and 95th percentile exposures for consumers, combining food consumption with the range of occurrence data for each food pattern defined. In doing that, the Expert Meeting took account of most situations that might exist throughout all stages of life, such as the variability of food consumption amounts and BPA concentrations in food for each possible food pattern.

Water was not considered as a stand-alone contributor; however, liquid consumption was taken into account in all scenarios. The concentration values assigned to liquid foods are similar to those for unpackaged drinking-water (maximum of 1 μg/l; see Table 1 above). In all modelling scenarios, it was assumed that there is no BPA in unpackaged food. Exposure from PC tableware was not included in the estimates, because, based on the maximum migration value reported (2 μg/l; see Table 1 above), it could be estimated that even using very conservative approaches (i.e. 100% consumption of packaged food prepared in tableware), tableware is a minor contributor to dietary exposure: approximately 0.1 μg/kg bw per day in infants 6–36 months of age.

For the purpose of this assessment, the "best-case estimate" means a scenario that results in the lowest realistic exposure. The "worst-case estimate" refers to a scenario that results in the highest exposure (i.e. the most conservative estimate).

3.2.1 Potential dietary exposure for infants 0–6 months of age

The potential dietary exposure for this age group needs to be assessed according to different possible consumption patterns. A range of possible scenarios may exist for feeding infants aged 0–6 months, as infants may be fed with liquid infant formula, powdered infant formula, breast milk or mixtures of these foods. In addition, the foods may be fed from bottles made of glass, metal or plastics, or infants may be exclusively breastfed. For the purpose of this assessment, it was assumed, after extensive review of the available data by the Expert Meeting, that the maximum BPA migration from PC bottles to be used in estimates was 15 μg/kg (see Table 1 above). This assumption was considered to be highly protective of consumers.

The Expert Meeting concluded that breastfed infants were exposed at the upper end of the range (mean and 95th percentile) to 0.3 and 1.3 μg/kg bw per day. When infants were fed with canned liquid formula in PC bottles, the estimates were 2.4 μg/kg bw per day at the mean and 4.5 μg/kg bw per day at the 95th percentile, whereas the estimates were lower, 2.0 and 2.7 μg/kg bw per day, respectively, for infants fed with powdered formula (prepared as consumed). When infants were fed with canned liquid formula in PC-free bottles, the estimates were 0.5 μg/kg bw per day at the mean and 1.9 μg/kg bw per day at the 95th percentile, whereas the estimates were lower, 0.01 and 0.1 μg/kg bw per day, respectively, for infants fed with powdered formula. The difference between the canned liquid and powdered formula is mainly caused by the migration of BPA from the epoxy resin coatings of the cans in which liquid formula is packaged.

The major sources of exposure in this age group are migration of BPA from PC bottles (81%) and infant liquid formula packaged in PC containers or metal cans with epoxy linings (19%). Migration of BPA from epoxy resin in contact with powdered milk formula contributes approximately 1% to exposure.

3.2.2 Potential dietary exposure for infants 6–36 months of age

The potential dietary exposure for infants 6–36 months of age was assessed allowing for a variety of food pattern scenarios because of the introduction of solid foods that occurs in this age group. In addition to consumption of liquid food (human milk or infant formula), the introduction of solid food, primarily packaged in glass with coated metal lids, was considered. All scenarios are based on an equal daily consumption of the following baby foods: fruits, desserts, vegetables and meat. Maximum concentrations of 7.2 μg/kg (see Table 1 above) were assigned to all infant foods to account for a high level of brand loyalty.

The Expert Meeting concluded that breastfed infants in this age group who also consumed solid food were exposed at the upper end of the range (average and maximum) to 0.1 and 0.6 μg/kg bw per day. When infants were fed with formula in PC bottles and solid food, the estimates were 0.6 and 3.0 μg/kg bw per day. When infants were fed with formula in PC-free bottles and solid food, the estimates were 0.1 and 1.5 μg/kg bw per day.

In these estimates, the potential dietary exposure to BPA due to migration from packaged solid food in glass containers capped with polymer-coated metal closures or small plastic containers for infants fed exclusively with these products ranged from <0.01 μg/kg bw per day at the mean (lowest value at 25% consumption of packaged food) up to 0.4 μg/kg bw per day at the maximum (highest value at 100% consumption of packaged food).

3.2.3 Potential dietary exposure for children over 3 years of age

For children over 3 years of age, it was assumed that the model diet is similar to that of adults, excluding the consumption of stimulants such as alcohol, coffee and tea. As for the previous age group, a budget method model was used to estimate exposure. In order to account for a variety of potential exposure situations, several scenarios were created according to different model diets, such as consumption of liquid and/or solid food (packaged or unpackaged).

For the lowest exposure scenario ("best case"), in which children are fed with 25% carbonated drinks and 25% solid packaged foods, estimates ranged from 0.2 μg/kg bw per day at the mean up to 0.5 μg/kg bw per day at the maximum.

For the highest exposure scenario ("worst case"), in which children are fed with 100% carbonated drinks and 100% solid packaged foods, estimates ranged from 0.7 μg/kg bw per day at the mean up to 1.9 μg/kg bw per day at the maximum.

The major source of exposure in this age group is migration from canned food (94%).

3.2.4 Potential dietary exposure for adults (including pregnant women)

As for the other population groups, budget method models were used to estimate exposure in adults (including pregnant women). Several scenarios were created according to different model diets, such as consumption of liquid and/or solid food (packaged or unpackaged). For solid and liquid food, a consumption based on an equal mixture was assumed: for solid food, a mixed diet of fruits, vegetables, grains, meat, soups, seafood and desserts; and for liquid food, a mix of stimulant drinks (coffee, beer, tea and alcohol).

For the lowest ("best case") exposure scenario, which is adults consuming 25% of their coffee, tea and alcoholic drinks and 25% of their solid food as packaged foods and beverages, estimates ranged from 0.4 μg/kg bw per day at the mean up to 1.0 μg/kg bw per day at the maximum.

For the highest ("worst case") exposure scenario, which is adults consuming 100% of their coffee, tea and alcoholic drinks and 100% of their solid food as packaged foods and beverages, estimates ranged from 1.4 μg/kg bw per day at the mean up to 4.2 μg/kg bw per day at the maximum.

Migration from liquid food is as important as migration from solid food.

3.3 Exposure from non-food sources

Based on the limited published or review data available on exposure to BPA from non-food sources, the Expert Meeting considered that the upper range of mean exposure from inhalation of free BPA (concentrations in indoor and outdoor air) is approximately 0.003 μg/kg bw per day for the general population. Indirect ingestion (dust, soil and toys) is considered to be approximately 0.03 μg/kg bw per day in infants and approximately 0.0001 μg/kg bw per day in children and adults. This is generally lower than exposure from food by at least one order of magnitude for most of the subgroups studied; in other words, the

Expert Meeting considered that food is by far the major contributor of overall exposure to BPA for most population groups.

Some additional potential sources of exposure have been identified, such as thermal papers and dental treatment. However, the Expert Meeting was unable to provide an estimate of exposure from thermal papers because of insufficient data on dermal absorption and observational studies on use patterns. For dental treatment, the Expert Meeting decided not to take this additional source into account in its estimates because exposure is short term and unlikely to contribute substantially to chronic exposure.

The dietary exposure estimates for the four population groups are summarized in Table 2.

Table 2. Summary of dietary exposure estimates from model diets for four population groups

Population	Source of exposure	Dietary exposure estimate (μg/kg bw per day)	
		Mean	95th percentile
Infants, 0–6 months	Exclusively breastfed	0.3	1.3
	PC bottles and formula[a] (powder–liquid)	2.0–2.4	2.7–4.5
	Formula, no PC bottles[a] (powder–liquid)	0.01–0.5	0.1–1.9
Infants, 6–36 months	Breastfed + solid food (best case–worst case)[b]	0.1	0.3–0.6[c]
	PC bottles and formula[a] + solid food (best case–worst case)[b]	0.5–0.6	1.6–3.0[c]
	Formula only, no PC bottles[a] + solid food (best case–worst case)[b]	0.01–0.1	0.1–1.5[c]
Children, 3+ years	Fruits, desserts, vegetables, meat, soups, seafood, carbonated drinks (best case–worst case)[b]	0.2–0.7	0.5–1.9[c]
Adults	Fruits, vegetables, grains, meat, soups, seafood, desserts, carbonated drinks, tea, coffee, alcoholic beverages (best case–worst case)[b]	0.4–1.4	1.0–4.2[c]

[a] Assumes formula only, no breast milk.
[b] Worst case is assuming the daily consumption of 100% packaged food and beverages, and the best case is assuming the daily consumption of 25% packaged food and beverages.
[c] Because of the use of the budget method model, maximum consumption is reported in these upper range of exposure estimates.

3.4 Conclusions and data gaps

The Expert Meeting drew the following major conclusions from the exposure estimates:

- In general, because of the conservative assumptions made, the estimated international exposures reported are higher than comparable national estimates.
- The average exposure of exclusively breastfed babies (0–6 months) to BPA was 0.3 μg/kg bw per day, and exposure at the 95th percentile was 1.3 μg/kg bw per day. Once solid foods are introduced (at 6–36 months), exposure to BPA decreases.
- There is a range of exposure estimates for infants fed with formula. Generally, exposure is higher for infants (0–6 months) fed with liquid formula than for infants fed with powdered formula and higher for infants fed using PC bottles than for infants fed using

non-PC bottles. The highest estimated exposure occurs in infants 0–6 months of age who are fed with liquid formula out of PC bottles: 2.4 µg/kg bw per day at the mean and 4.5 µg/kg bw per day at the 95th percentile.

- For children older than 3 years, highest exposure estimates did not exceed 0.7 µg/kg bw per day at the mean and 1.9 µg/kg bw per day at the maximum.
- For adults, highest exposure estimates did not exceed 1.4 µg/kg bw per day at the mean and 4.2 µg/kg bw per day at the maximum.
- Based on the limited data available, exposure to BPA from non-food sources is generally lower than that from food by at least one order of magnitude for most subgroups studied. In other words, food is by far the major contributor of overall exposure to BPA for most population groups.
- Some additional potential sources of exposure (unpackaged food and thermal paper) have been identified. However, the Expert Meeting was unable to provide exposure estimates owing to insufficient data.

The following data gaps were identified:

- BPA concentrations in unpackaged foods;
- data on the consumer use patterns for materials and products containing BPA, including specific geographical differences; and
- the contribution of dermal exposure to overall exposure.

4. Metabolism and toxicokinetics

The toxicokinetics (or pharmacokinetics) of orally and parenterally administered BPA has been studied in rodents, non-human primates and humans. BPA is extensively absorbed from the gastrointestinal tract, consistent with its substantial aqueous solubility (0.5–1.3 mmol/l) and lipophilicity (log octanol–water partition coefficient = 2.2–3.4). BPA undergoes substantial presystemic Phase II metabolism in the gut and liver following oral administration (absolute bioavailability 0.9–1.9% in adult and neonatal non-human primates, respectively, and 2.8% in adult rats), primarily to the glucuronide conjugate. Conversion to the glucuronide conjugate is critical because, unlike the aglycone form of BPA, it does not bind to the estrogen receptor (see section 5). In rodents, BPA glucuronide is subjected to biliary excretion, enterohepatic recirculation and principally faecal excretion; non-human primates and humans quantitatively excrete conjugated forms of BPA in urine within 6 h, consistent with BPA's short half-life (<2 h for urinary excretion; Völkel et al., 2002; J.G. Teeguarden et al., unpublished data submitted to WHO). Available serum and tissue toxicokinetic evidence from single and repeated-dose administration shows that aglycone BPA does not accumulate in the body.

Despite some differences between BPA metabolism and disposition in rodents and primates, internal exposures to aglycone BPA are remarkably similar for adult rodents, non-human primates and humans. This apparent lack of requirement for allometric scaling is atypical in the therapeutic drug and general chemical literature and suggests that a specific adjustment for interspecies differences in toxicokinetics is not required.

Significant age-dependent changes in Phase II metabolic capability are evident in neonatal rodents. Internal exposures (area under the curve, maximum plasma concentration) of neonatal rats to aglycone BPA exceed those observed in a neonatal non-human primates

study at identical doses. In a recent study there was an approximately 4-fold difference in the AUC of aglycone BPA between neonatal (PND 5) and adult non-human primates, however, this difference did not reach statistical significance.

Lactational transfer in rats appears to be limited, such that exposures of suckling rat neonates are 300- to 500-fold lower than maternal or direct oral dosing, respectively. Placental transfer occurs almost exclusively for aglycone BPA, and the fetal levels in rats are in the same range as those in other maternal tissues. Fetal levels of aglycone BPA decline with gestational developmental changes in fetal tissue composition and development of Phase II capabilities.

BPA exposure in adult humans, estimated from total urinary excretion information from the United States National Health and Nutrition Examination Survey (NHANES) and other studies (upper range of median values of approximately 0.05 μg/kg bw per day; see section 6.1), has been used as the basis for physiologically based pharmacokinetics (PBPK)–based predictions of steady-state circulating levels of aglycone BPA of approximately 0.0004 nmol/l (0.1 ng/l). This prediction of very low internal exposures to the biologically active form of BPA is consistent with well-controlled biomonitoring (see section 6.1) and pharmacokinetic studies that show undetectable levels of aglycone BPA in human serum (limits of detection: 1.2 nmol/l, J.G. Teeguarden et al., unpublished data submitted to WHO; and 10 nmol/l, Völkel et al., 2002).

In conclusion, information is available to define lactational and placental transfer and neonatal, child and adult exposures to the active aglycone form of BPA. Lactational transfer in rats appears to be limited, fetal exposure is dominated by maternal factors, differences in internal exposure to aglycone BPA between children and adults are not large, and variability among adults is unexplored. The impact of different routes of administration (i.e. parenteral versus oral) is critical based on the dominance of first-pass Phase II metabolism of BPA in the gut and liver. The effect of repeated oral dosing on blood and tissue accumulation appears to be minimal and consistent with single-dose kinetics.

The extensive data from fetal, neonatal and adult experimental animals in conjunction with human pharmacokinetic and biomonitoring data have prompted the development of several PBPK models. These models have estimated circulating concentrations of aglycone BPA to be in the picomole per litre range for children and adults with no identified sources of exposure. The continuing goal is to use PBPK modelling to provide more refined estimates of aglycone BPA concentrations in potential target tissues of developing fetuses, children and adults from oral and other routes of exposure to minimize uncertainty in risk assessment for BPA exposures from foods and beverages, medical devices and other environmental sources.

The major remaining research need is additional human pharmacokinetic studies performed to high standards of analytical sensitivity and method validation that provide accurate and precise time-dependent measurements of aglycone and conjugated forms of BPA in conjunction with complete analysis of urinary excretion. These data are essential for filling some identified data gaps and thereby minimizing uncertainty through mass balance evaluation as well as classical pharmacokinetic and PBPK modelling approaches to human metabolism and disposition of BPA.

5. Biological activities of BPA

Many of the physiological effects of BPA have been described in the context of the ability of the active aglycone form to interact with classic estrogen receptors. BPA can have estrogenic activity, but it should not be considered to act only as an estrogen or even a selective estrogen receptor modulator. Depending on the system studied and the dose, BPA may exert pleiotropic cellular and tissue-type specific effects and can exhibit non-monotonic dose–response relationships at cellular and intracellular levels.

When BPA acts as a ligand of the nuclear estrogen receptors, the influence on responsive genes is not identical to that of endogenous estrogens (e.g. 17β-estradiol) or other natural or synthetic ligands (e.g. diethylstilbestrol [DES]). Comparison of gene-centric data for BPA with those of estradiol and two potent estrogenic compounds (17α-ethinylestradiol and DES) lends additional support for this conclusion. In one study the transcriptomal signature profiles of MCF7 cells were compared following a 48 h incubation with estradiol at 30 pmol/l or BPA at 10 nmol/l; messenger ribonucleic acid levels of a similar number of genes were changed following treatment with BPA (2102 genes) and estradiol (2164 genes), but only 668, or approximately 30%, were affected in common.

A large number of in vitro studies have helped elucidate specific molecular interactions of BPA in cell systems. In vitro studies summarized in Wetherill et al. (2007) used female reproductive tissue (lowest-observed-effect concentrations [LOECs] 0.0001–0.1 μmol/l), breast cancer cells (LOECs 0.0001–1 μmol/l), male reproductive tissue (LOECs 0.0001–150 μmol/l), pancreatic/adipose tissue (LOECs 0.0001–10 μmol/l), pituitary tissue (LOECs 0.000 001–1 μmol/l), neural cells or tissues (LOECs 0.000 000 1–2.5 μmol/l), immune cells (LOECs 0.0001–10 μmol/l) and embryonic cultures (LOECs 0.1–1 μmol/l). The estrogenic potency of BPA ranges over about 8 orders of magnitude but is generally 1000-fold less than that of positive control estrogens in vitro and 1000- to 10 000-fold less based on in vivo models (Chapin et al., 2008).

During activity testing under Phase 1 of the United States Environmental Protection Agency's (USEPA) ToxCast™ (467 high-throughput screening assays), BPA had measurable activity in 101 assays involving signalling pathways for estrogen, androgen and thyroid, as well as other nuclear receptors (e.g. glucocorticoid receptor, peroxisome proliferator-activated receptor, pregnane-X receptor) and xenobiotic metabolizing enzymes that have potential relevance to endocrine signalling (cytochrome P450s [CYP], including aromatase). The three main gene targets at half-maximal activity concentration (AC_{50}) values below 10 μmol/l are estrogen receptor 1 (ESR1, also referred to as estrogen receptor alpha), xenobiotic sensing and metabolizing CYP enzymes, as well as down-regulation of a number of inflammatory response genes in assays using human primary cell lines. Indications of whole cell toxicity (e.g. cell cycle arrest, reduced hepatic cell viability, stress kinase) and genotoxicity were seen at high concentrations, generally with AC_{50} values in excess of 100 μmol/l.

Exposure to BPA in utero (oral doses of 50 mg/kg bw, and other than oral routes of exposure) has been shown to affect the methylation status and expression of several differentially methylated promoters, raising the possibility that BPA also acts through mechanisms resulting in alteration of CpG methylation (Ho et al., 2006; Dolinoy et al., 2007; Bromer et al., 2010).

In conclusion, the available data show that BPA's biochemical and molecular interactions are complex, involving classic estrogen receptors and also a variety of other receptor systems and molecular targets. It is unclear if all observed effects can occur in vivo, at concentrations relevant to human exposure, and if observed changes can lead to adverse health outcomes. The complexity of BPA's interactions and concentration ranges at which the observations have been made make it challenging to conclude whether a given in vivo finding is biologically plausible based on consistency and potency of a response compared with estrogens alone. Dose–response analyses may be useful to identify the involvement of multiple receptor/signalling pathways that is typical of complex physiological end-points.

The Expert Meeting recommends that, whenever possible, concurrent controls with relevant doses for effect detection be considered in experimental design when hypotheses include or assume involvement of specific mechanisms or modes of action of BPA.

6. Human data

6.1 Biomonitoring data

The internal BPA dose in humans can be estimated by measuring unconjugated (free) and conjugated (i.e. glucuronidated and sulfated) BPA levels in biological tissues or fluids. Urinary concentrations of total (free plus conjugated) BPA, particularly in spot samples, have often been used to estimate exposure. Available data from biomonitoring studies in North America, Europe and South-east Asia suggest that human exposure to BPA is widespread across the lifespan in these parts of the world (Becker et al., 2009; He et al., 2009; CDC, 2010; Health Canada, 2010; Völkel, Kiranoglu & Fromme, 2010). Although the average total BPA concentrations in selected populations of North America, Europe and South-east Asia are comparable (i.e. ~1–3.7 μg/l), some differences exist. These differences may be related to differences in exposures across geographical areas, study designs or analytical methods used.

BPA biomonitoring concentrations represent an integrative measure of exposure from multiple sources and routes. To assess exposure, most biomonitoring studies have relied on measuring the concentrations of total BPA in human urine. To obtain biomonitoring-based exposure estimates, the total BPA urinary concentrations were multiplied by the age-specific estimated 24 h urinary output volume (ml) (presumed to be equivalent to the daily exposure) and divided by body weight (NTP, 2008; Becker et al., 2009; Völkel, Kiranoglu & Fromme, 2010). Using these assumptions, the biomonitoring-based median exposure estimates are in the range of 0.01–0.05 μg/kg bw per day for adults and somewhat higher (0.02–0.12 μg/kg bw per day) for children. The 95th percentile exposure estimates are 0.27 μg/kg bw per day for the general population and higher for infants (0.45–1.61 μg/kg bw per day) and children 3–5 years of age (0.78 μg/kg bw per day) (NTP, 2008; Becker et al., 2009; Völkel, Kiranoglu & Fromme, 2010). These estimates are comparable to estimates based on food consumption amounts and levels measured in food or model calculations, which are often based either on worst-case assumptions or on limited knowledge of the variety or extent of external exposure pathways.

When investigating the absorption, distribution, elimination and metabolism of BPA in humans or when conducting a human health risk assessment, concentrations of BPA in blood may be of interest. However, because BPA has a relatively short elimination half-life, BPA concentrations in blood are considerably lower than those in urine and decrease quickly after

exposure. Moreover, it is difficult to rule out cross-contamination with trace levels of free BPA during sample collection, storage and analysis because of the ubiquitous presence of BPA in the environment, including materials in contact with blood samples. Therefore, because of these current technical limitations, concentrations of BPA in blood have limited value for epidemiological studies at present, in particular where a considerable number of reliable detectable observations are required to achieve adequate statistical power. Efforts are under way to improve measurements of BPA in blood.

The Expert Meeting identified the following data gaps and made recommendations to address them:

- Biomonitoring data are largely limited to North America, Europe and South-east Asia. Additional studies should evaluate exposure in all geographical areas and also among specific population groups.
- Biomonitoring data suggest human exposure to BPA across the lifespan, but information on fetal and early-life BPA exposure is limited. Studies are needed to determine whether measurements of BPA concentrations in maternal biological specimens are adequate surrogates for fetal and infant exposures. Furthermore, the usefulness of non-conventional matrices (e.g. amniotic fluid, cord blood) to assess fetal exposure to BPA needs to be evaluated. Also, issues related to potential matrix cross-contamination (e.g. amniotic fluid and blood) need to be evaluated to ensure the integrity of the biomonitoring specimen.
- As BPA is a ubiquitous environmental contaminant, careful attention is required to avoid external contamination during sampling and analysis, particularly when measuring unconjugated (free) BPA concentrations. Studies should be conducted to identify additional environmental sources of exposure to BPA and their potential contribution during sampling and analysis of biological specimens for biomonitoring purposes. A detailed description of the sample collection protocols, including sampling location and procedures, sample handling and storage conditions, should be included in all biomonitoring studies. To monitor for potential external contamination, laboratory blanks and field blanks are needed.
- Urinary concentrations of total BPA (free and conjugated) are adequate exposure biomarkers. However, because of BPA's short elimination half-life (<2 h for urinary excretion), strategies to address the large variability in BPA concentrations of spot urine samples need to be developed to adequately categorize exposure as appropriate to the end-point of interest. When the population investigated is sufficiently large (e.g. nationally representative population-based surveys), the spot sampling approach may provide enough statistical power to categorize the average population exposure to BPA. For purposes other than population-based surveys, biomonitoring data would be strengthened with the collection of multiple (rather than single) spot urine samples, particularly in studies aimed at evaluating the potential impact of exposure to BPA on human health. Furthermore, the study design should consider the impact of time of day of sampling (e.g. in relation to consumption of food) and time of last urination as important exposure contributors to provide the best approach for BPA exposure assessment.
- Research is needed to identify biomarkers for long-term exposure to BPA. If such biomarkers are identified, validated protocols for their measurement for biomonitoring purposes need to be developed.
- In addition to complying with the requirements set forth in regards to the analytical methodology for measuring BPA in biological specimens (e.g. urine, blood), the following additional considerations are needed to generate and interpret valid biomonitoring data:

- Although cross-contamination with BPA can occur with any matrix, including urine, the impact of trace contamination of urine with BPA will likely be less critical than for other biological matrices (e.g. blood) as a result of the higher detectable levels in urine than in these other matrices.
- The potential contamination with BPA of archived human specimens must be evaluated (e.g. by measuring BPA conjugates) if these specimens are to be used for BPA biomonitoring purposes.
- When measuring concentrations of total (free plus conjugated) BPA, appropriate surrogate standards are needed to monitor the extent of the deconjugation reaction.
- Properly characterized quality control materials must be analysed and their concentrations evaluated according to standard statistical probability rules, along with the target samples, to monitor the method precision and accuracy.

6.2 Epidemiological studies

There are a limited number of epidemiological studies, with the majority using cross-sectional designs and a single measure of urinary BPA. Cross-sectional studies concurrently assess BPA exposure and health outcome, thus limiting their interpretability, especially for outcomes that have long latency periods (e.g. cardiovascular disease [CVD], diabetes).

Given the short half-life of BPA, the use of a single urine sample to categorize exposure is also a limitation, especially for studies of health outcomes with more temporally distant etiological windows of exposure. Most studies were relatively small and have limited power to achieve statistical significance for exposure–outcome associations. However, when there were multiple studies reporting consistent directions of associations for a given health outcome that were consistent with the animal toxicology, we considered this suggestive evidence of associations.

Unmeasured factors may confound potential BPA–outcome associations and bias effect estimates from epidemiological studies. This concern may be overstated in cases when the confounding factor is not associated with BPA exposure or the outcome.

6.2.1 Reproductive end-points

6.2.1.1 Semen quality

Three epidemiological studies investigated the association of urinary BPA concentrations with semen quality. Studies varied in their sample population: men who were partners of pregnant women in the USA (“fertile men”) (Mendiola et al., 2010), male partners in infertile couples that were patients in an infertility clinic (“male partners in infertile couples”) (Meeker et al., 2010) and workers with occupational exposure to BPA in China (“Chinese workers”) (Li et al., 2010). All three studies, although of relatively modest sample size (ranging from 190 to 302 men), reported associations of increased urinary BPA concentration with one or more measures of reduced semen quality. Among Chinese workers, both occupational exposure (median urinary BPA concentration = 38.7 μg/l) and environmental exposure (median urinary BPA concentration = 1.4 μg/l) were associated with reduced sperm concentration and total sperm count, whereas reduced sperm motility was associated only with high occupational exposure. Among fertile men (n = 302), associations of urinary BPA concentration (median = 1.7 μg/l) with semen quality measures were not statistically significant, but were suggestive of inverse associations with total sperm count, total motile

count and percent motile sperm (Mendiola et al., 2010). Among male partners in infertile couples (n = 167), there were positive associations (although not statistically significant) between urinary BPA concentration (median = 1.3 μg/l) and odds of being below the WHO reference sperm concentration, total sperm count and sperm motility. In addition, there was a positive association of urinary BPA concentrations with abnormal sperm morphology (Meeker et al., 2010).

In conclusion, the associations of urinary BPA with semen quality were consistent across the three studies; higher urinary BPA concentration was associated with lower semen quality. The strengths of the three studies include the use of different study populations of men with adjustment for some relevant confounders. Limitations include the cross-sectional designs, incomplete assessment of occupational co-exposure in the Chinese cohort study and lack of a statistically significant association in two of the studies.

Given the limited human and toxicological evidence, further study on the association of BPA with semen quality is recommended. To account for within-person variability in both semen quality and exposure to BPA, recommended study designs include collecting multiple urine and semen samples from each man enrolled in the study.

6.2.1.2 Ovarian response

One small study (n = 84) reported an association of urinary BPA concentration (median = 2.6 μg/l) with reduced oocyte yield and peak serum estradiol among women undergoing treatment with in vitro fertilization (Mok-Lin et al., 2010).

Conclusions based on this single small study are not possible without replication.

6.2.2 Puberty

Two epidemiological studies, one small (n = 192) cross-sectional study (Wolff et al., 2008a) and one large (n = 1151) prospective cohort study (Wolff et al., 2010), did not find consistent evidence of an association of urinary BPA concentration (geometric mean = 1.0–2.4 μg/l in the first study; median = 2.0 μg/l in the second study) with altered age of pubertal onset among girls. However, in the cross-sectional study (Wolff et al., 2008a), there was a suggestive trend of later onset of breast development with higher urinary BPA concentration.

In conclusion, the evidence for an association of BPA with altered age of pubertal onset in girls is limited and inconsistent. Research needs include large prospective studies on the association of BPA with pubertal development. A research gap is the lack of studies on male pubertal development in relation to BPA exposure.

6.2.3 Growth and neurodevelopment

Three published epidemiological studies have examined the association of BPA with perinatal outcomes, body mass index (BMI) and neurodevelopment. One study (n = 40) examining perinatal outcomes relied on a single serum measure of BPA (median = 5.9 μg/l) at birth (Padmanabhan et al., 2008); the other (n = 367) relied on a single urinary BPA concentration (median = 1.3 μg/l) in the third trimester of pregnancy (Wolff et al., 2008b). Wolff and colleagues (Wolff et al., 2008b) found that urinary BPA concentrations in pregnant women in the third trimester were associated with modest elevations (although not

statistically significant) in birth weight. There is only one cross-sectional pilot study (n = 90) examining the association of urinary BPA concentration (median = 2.0 μg/l) with BMI (Wolff et al., 2007).

It is difficult to draw any conclusions from these studies because they were cross-sectional, relied on a single measure of exposure or did not adequately adjust for important potential confounders. Further research examining the association of serial measures of urinary BPA concentrations in pregnant women would be valuable to determine whether BPA is a risk factor for adiposity, BMI or perinatal end-points.

Only one prospective cohort study (n = 249) has examined the relationship of serial BPA urinary concentrations in pregnant women (median = 2.0 μg/l) with neurobehavioural outcomes (Braun et al., 2009). This study found a positive association between urinary BPA concentrations measured during pregnancy and externalizing behaviours (i.e. aggression and hyperactivity) using the Behavioural Assessment System for Children-2 (BASC-2). The effect was stronger among 2-year-old girls, and the association was consistently stronger, for urinary BPA concentrations measured during early pregnancy. In an unpublished follow-up of 3-year-old children (n = 237) from this same cohort (J.M. Braun et al., unpublished data submitted to WHO), the investigators found persistent associations of mean prenatal urinary BPA with externalizing behaviours using the BASC-2. At the 3-year follow-up, the investigators also reported associations of prenatal urinary BPA concentrations with internalizing behaviours among girls and executive functions, using the Behavior Rating Inventory of Executive Function (Preschool Version) (BRIEF-P), in the total sample (J.M. Braun et al., unpublished data submitted to WHO). Finally, there was a positive association between prenatal urinary BPA concentration and the Anxiety Subscale of the BASC-2, a key end-point observed in animal toxicology studies (see section 7.5). These associations remained after adjustment for a variety of confounders, including prenatal cotinine and phthalate exposures.

This study suggests that prenatal BPA exposures—especially those that occur during early pregnancy—are associated with the later development of behavioural problems in children. Replication of this study using large prospective birth cohorts with serial measures of urinary BPA collected during pregnancy, especially those taken during early gestation, is a high-priority research need.

6.2.4 Cardiovascular disease and diabetes

Two cross-sectional analyses of NHANES data reported associations of BPA exposure (median 2.5 and 1.8 μg/l) with self-reported diagnosis of pre-existing CVD and diabetes (Lang et al., 2008; Melzer et al., 2010). These cross-sectional analyses have several important weaknesses that limit their interpretation. A major limitation is the use of a single spot urine sample collected concurrent with information on self-reported diagnosis of CVD and diabetes. The single urine sample reflects recent BPA exposure only (past several hours) and may not adequately measure BPA exposure during the relevant etiological window for CVD and diabetes, which might be years or decades earlier.

Conclusions based on these cross-sectional analyses are not possible. Prospective studies with serial exposures to BPA assessed during etiologically relevant windows, years before development of CVD and diabetes, are needed.

7. Toxicology

7.1 Acute and repeated-dose toxicity

BPA has been tested in a variety of species, using multiple standard protocols, to ascertain the potential acute, short-term and subchronic toxicity that may occur following exposure. The available data suggest that BPA is of low acute toxicity. With regard to repeated exposures, Tyl et al. (2002, 2008) conducted two large multigenerational studies in rats and mice using dietary administration of BPA over a wide range of doses (1 or 3 µg/kg bw up to 500 or 600 mg/kg bw), allowing for dose–response assessment. These studies demonstrated effects on the liver, kidney and body weight at doses of 50 mg/kg bw and higher. A more recent study by Stump et al. (2010), which also used an expanded dose range and the same animal model as that used by Tyl et al. (2002), demonstrated similar findings (on common end-points examined), with a lowest no-observed-adverse-effect level (NOAEL) of 5 mg/kg bw. The liver also appeared to be a target organ in a non-rodent model (dog), with a NOAEL of 74 mg/kg bw following oral exposure.

There are no long-term toxicity studies with BPA other than the carcinogenicity studies discussed in section 7.3 below.

In conclusion, BPA is of low acute toxicity, and the lowest NOAEL for subchronic exposure currently available is approximately 5 mg/kg bw per day, as identified in several studies. No research needs were identified in this area.

7.2 Genotoxicity

Studies of the potential of BPA to induce mutations, chromosomal aberrations, sister chromatid exchange and transformation in a variety of in vitro test systems are largely negative, including studies with *Salmonella typhimurium*, Chinese hamster V79 cells, Syrian hamster embryo cells and mouse lymphoma cells (NTP, 2008). However, deoxyribonucleic acid (DNA) damage was induced by BPA in MCF-7 and MDA-MB-231 cells (Iso et al., 2006). DNA adduct formation in Syrian hamster ovary cells (Tsutsui et al., 1998, 2000) and a number of positive findings have been reported for the potential for BPA to inhibit purified microtubule polymerization, affect the spindle apparatus and produce aneuploidy in in vitro studies with Chinese hamster V79 cells or oocytes from Balb/c or MF1 mice (NTP, 2008). Although BPA can affect chromosomal structure during replication in in vitro studies, the outcomes of similar assessments when the chemical is administered to laboratory mice are inconsistent and inconclusive. The striking findings of meiotic aneuploidy in oocytes of mice (Hunt et al., 2003; Susiarjo et al., 2007) have not been independently replicated, and the failure to observe clear effects on fertility or cancer associated with BPA exposures during development suggests that the findings are of limited biological significance.

In conclusion, BPA is not a mutagen in in vitro test systems, nor does it induce cell transformation. BPA has been shown to affect chromosomal structure in dividing cells in in vitro studies, but evidence for this effect in in vivo studies is inconsistent and inconclusive. BPA is not likely to pose a genotoxic hazard to humans.

7.3 Carcinogenicity

In the traditional rodent cancer bioassay (NTP, 1982), BPA at doses of approximately 75–150 mg/kg bw per day gave, at best, weak evidence of carcinogenic activity, but it is questionable whether the chemical was adequately studied. The United States National Toxicology Program (NTP) bioassay did not include exposures during the perinatal period, which would appear to be a critical window of exposure. Studies that included perinatal (gestational and/or lactational) exposures to BPA (oral doses to the dam from ~10 to 250 µg/kg bw per day) have reported, among other lesions, proliferation of mammary ductal epithelium and squamous metaplasia of prostatic epithelium in offspring, conditions thought by many to predispose to neoplasia (Timms et al., 2005; Moral et al., 2008). Additional treatments with initiating or promoting agents have led to earlier onset of mammary tumours (Jenkins et al., 2009) or prostatic intraepithelial neoplasia (Prins et al., 2010).

However, the studies that included exposures to BPA during the appropriate periods all suffered from one or more deficiencies in design or execution that prevent a definitive evaluation of its potential as a carcinogen. These include 1) lack of consideration of litter effects, 2) small numbers of animals, 3) insufficient study duration to determine whether developmental conditions thought to enhance cancer susceptibility actually did so and 4) additional treatment with a strong initiating or additional promoting agent(s). In the absence of additional studies addressing these deficiencies, there is currently insufficient evidence on which to judge the carcinogenic potential of BPA.

The Expert Meeting was aware of a rodent cancer study about to begin at the National Center for Toxicological Research, United States Food and Drug Administration (USFDA), under the auspices of the NTP. This study, to be conducted in compliance with good laboratory practice, is designed to include a wide oral dosing range, beginning during gestation, continuing with direct dosing during the neonatal period and extending through 2 years. It is intended to address and measure developmental changes in a variety of end-points that have been reported in more limited studies and allow full expression of their potential to manifest as disease and disability later in life. The study will fully characterize internal exposures to free and conjugated BPA.

7.4 Reproductive and developmental toxicity of BPA in mammalian species

Over the last several decades, there have been hundreds of experimental studies on the potential reproductive and developmental toxicity of BPA in laboratory and domestic animal species, the large majority of the studies being conducted with rats and mice. In fact, all of the new, low-dose studies that administered BPA orally, the most relevant route of exposure, were conducted using laboratory rodents. These studies have been reviewed recently by several regulatory bodies, and most have identified an oral reproductive and developmental NOAEL of 50 mg/kg bw per day.

In spite of these reviews and the large number of animal studies, there remains considerable debate about the potential for low-dose effects of BPA in humans. The Expert Meeting considered the "new" studies since 2008 and the more recent USFDA draft review of BPA and integrated these with the existing data to provide an overall summary of the potential low-dose effects of BPA that may be relevant to human health. The 1 mg/kg bw per day dose level was selected as the cut-off for "low" dosage levels, as human exposures to BPA occur in the microgram per kilogram of body weight per day dose range and to clearly distinguish

effects occurring in this range from those that are seen in rodent studies at "high" dosage levels—that is, levels that are irrelevant to the majority of non-occupational human exposures. BPA doses above 5 mg/kg bw per day were considered to be "high" dose levels, as this is the NOAEL used by most regulatory agencies. This NOAEL is based upon adverse systemic effects that occur at doses below the 50 mg/kg bw per day NOAEL for reproductive and developmental toxicity.

Where the only evidence for adverse effects of BPA comes from studies in rats or mice and other animals with no relevant conclusive evidence from humans or non-human primates, account needs to be taken of key species differences that may limit straightforward translation of findings from rodents to humans. Rodents are born in a relatively immature state compared with humans and could therefore be vulnerable after birth to developmental effects that would occur prenatally in humans (and thus be governed by maternal exposure). For example, prostate differentiation occurs at around birth in rodents (mainly post-birth), whereas it occurs in mid-pregnancy in humans. Masculinization of the hypothalamic–pituitary–gonadal (HPG) axis (some aspects of which can be termed defeminization) occurs around birth in rodents. In the male rodent, this process is partially mediated by estradiol produced locally in the brain from circulating testosterone. Disruption of HPG differentiation in the neonatal female rat can alter the timing of puberty, estrous cyclicity and fertility, for example. Similarly, disruptions of some aspects of male-specific hypothalamic–pituitary function in neonatal male rats can impinge on development and function of the testis and reproductive tract later in life. In contrast, in human males, the comparable events in the brain are initiated in the third trimester of pregnancy and are driven primarily by androgens, with no involvement of estrogens. A further contrast is that the earliest steps in spermatogenesis in rodents are initiated shortly after birth and progress to full spermatogenesis by 6–8 weeks, whereas these events are delayed until 12–15 years of age in boys. Similarly, in female rodents, maturation of the HPG components that regulate estrous cyclicity is complete by 15 days of age, whereas this event (menarche) is delayed until 10–12 years of age in girls.

Therefore, it is important to allow for species differences in timing of key critical developmental periods of sexual differentiation and to consider the role of different hormones in this process in extrapolating the effects of BPA from rodents to humans.

The Expert Meeting reached the following conclusions about the potential of low doses (<1 mg/kg bw per day) of BPA administered by the oral or subcutaneous route to alter reproduction and development in rodents:

- There was sufficient evidence to conclude that BPA does not:
  - induce gross morphological reproductive abnormalities in F_1 offspring;
  - reduce F_1 pup survival or body weight;
  - alter F_1 growth or survival during lactation;
  - alter F_1 anogenital distance in males or females;
  - cause undermasculinization of male morphology or masculinization of female morphology.

- There is evidence (with some uncertainty) that BPA does not:
  - reduce P_0 implantation, infertility or fecundity.

- There is conflicting evidence (with higher uncertainty) that BPA:

- alters F_1 pubertal landmarks in males or females. Most of the uncertainty centres on the effects of BPA on puberty, the age at first estrus, in the mouse;
- alters P_0 male or female reproductive tract organ weights or histopathology;
- alters hormone levels in P_0 or F_1 males or females. The literature was inconsistent, but most studies were negative;
- alters F_1 male reproductive tract organ weights or histopathology and semen parameters. There is great uncertainty as to whether BPA exposure alters some of these end-points (primarily for the prostate and mammary glands).

The Expert Meeting concluded that there is considerable uncertainty as to whether BPA has any effect in rodents on conventional reproductive or developmental endpoints at doses below 1 mg/kg bw per day by the oral or subcutaneous route.

Important data gaps in the reproductive and developmental toxicology of BPA in experimental animals include the following:

- a thorough assessment of critical developmental reproductive end-points following direct exposure of the neonate to BPA; and
- a thorough assessment of the effects of BPA in alternative animal models, including non-human primates, lagomorphs and other non-rodent species, that might be more relevant to human development for a few specific issues (e.g. effects on the prostate).

7.5 Neurobehavioural, neurotoxic and neuroendocrine effects

Neurological studies in laboratory animals (rat, mouse, sheep and/or non-human primate) assayed pathology, neurochemistry, neuroendocrine system, sensory systems, locomotor and spontaneous activity, social and sexual behaviours, anxiety, and learning and memory at various stages of development. Exposure was primarily during the periods of gestation and lactation.

The experimental evidence does not support brain developmental neuropathological changes (e.g. cortical thickness, cerebellum height, height of hippocampal layers) at rat maternal dietary exposures below 164 mg/kg bw per day (Stump et al., 2010). No further work in this area is needed. Brain biochemical changes (e.g. monoaminergic, cholinergic, glutamatergic, nuclear receptor expression and signalling) were reported in rodents at dietary exposures below 5 mg/kg bw per day, although these studies had methodological shortcomings and often lacked the concurrent assessment of a functional correlate, thus limiting their interpretability.

In general, only a small body of work has specifically focused on the impact of BPA on morphometric and cellular brain sex differences, and effects are region specific. Depending on the hypothesized mode of action, not all studies included both sexes. In some cases, only one sex was impacted, whereas in others, the overall differences between the sexes were reduced or eliminated. Limitations in the study designs increase uncertainty in interpretation (reviewed in Wolstenholme, Rissman & Connelly, 2010).

BPA does not appear to affect sensory systems, spontaneous activity or female sexual behaviour in rodents. For neonatal reflexes, sensory response, spontaneous motor activity and other open field behaviours, a minimum NOAEL of 164 mg/kg bw per day for rat maternal dietary exposure can be identified. Minimum NOAELs (corresponding to the highest dose

tested in individual studies) of 200 µg/kg bw per day (Ryan et al., 2010) and 320 mg/kg bw per day (Kwon et al., 2000) for rodent maternal dietary exposure could be identified for lordosis; for other components of sexual/sociosexual behaviours, NOAELs could not be identified. For learning and memory in rodents, conflicting data exist, although the weight of evidence does not suggest these to be a concerning hazard identification end-point.

There was uncertainty with regard to the interpretation of the data on anxiety (rodent and non-human primate) as a behavioural end-point owing to study design limitations, including testing apparatus, inclusion of only one sex, age at examination and non-oral route of administration. Additionally, although the available data suggest a decrease in sexual dimorphism within anxiety end-points, the toxicological significance was uncertain. The uncertainty centred on whether elimination of sexual dimorphism without statistically significant changes within individual sexes could be considered adverse (e.g. Ryan & Vandenbergh, 2006; Gioiosa et al., 2007). The weight of evidence does not provide for the determination of a NOAEL, but the data do demonstrate that anxiety, with its known sexually dimorphic attributes, is a potential hazard identification end-point requiring additional study, particularly with regard to a dose–response relationship. Mechanistic data have yielded some information regarding a potential mode of action. Monoamine pathways have been implicated in anxiety-related behaviours. Available mechanistic data suggest that perinatal exposure to BPA may lead to alterations in dopamine signalling pathways, including synthesis, release, uptake and receptor activation, but these studies have design limitations, including small sample size, non-oral route of administration and narrow dose ranges. An unpublished follow-up to a prospective cohort study examining internalizing and externalizing behaviours, including anxiety, in children is described in section 6.2.

Neuroendocrine data in rodents and sheep suggest effects on female HPG axis organization (≥50 µg/kg bw per day, non-oral route) and function (≥5 mg/kg bw per day, non-oral route). The specific mechanisms by which this occurs remain to be identified, but some data suggest that the pattern of luteinizing hormone release may be altered by exposure, resulting in blunted secretion and resistance to feedback.

In conclusion, developmental exposure to BPA does not appear to affect sensory systems, spontaneous activity or female sexual behaviour in laboratory animals. Changes in brain biochemical signalling, morphometric and cellular end-points within sexually dimorphic anatomical structures and neuroendocrine end-points were reported at dietary exposures below 5 mg/kg bw per day. Importantly, methodological limitations introduce uncertainty in interpretation of the findings. Based on the available data, changes in anxiety and convergence of anatomical brain sex differences were identified as end-points suggestive of effects with potential human relevance, but where further investigation is necessary to address uncertainty.

Additional study is needed to examine anxiety-related behavioural end-points (and the underlying mechanisms) following developmental exposure. To decrease the uncertainty in interpretation of the available data and provide data to better characterize the potential toxicity (adversity) resulting from convergence of brain sex differences, the following studies are recommended:

- employing multiple validated protocols for anxiety testing (e.g. plus maze, light/dark box, zero maze) using multiple doses in both sexes;

- testing at multiple ages, taking into consideration recognized age-dependent changes on anxiety and related behaviours in both sexes;
- examining the association of impacts on brain sex differences with functional (behavioural or physiological) end-points; and
- conducting dose–response analysis for anatomical brain sex differences in both sexes.

7.6 Other effects

7.6.1 Immunotoxicity

Several studies have examined BPA's ability to modulate the immune response using a variety of protocols, animal models, and ex vivo and in vitro assays. The overall ability of the immune system to respond or be sensitized following exposure to BPA is in the early stages of investigation. The results of rodent studies using direct or in utero exposure and repeated-dose protocols suggest that BPA may modulate immune homeostasis (cytokine activity, macrophage nitric oxide synthesis, tumour necrosis factor-alpha secretion, T helper 1/2 cell shifts). Several of these studies also examined spleen and thymus weights or histopathology, with reported immune responses occurring in the absence of observed changes in these organs.

As noted in previous reviews, various studies (patch test, modified Landsteiner and non-traditional protocols) have examined BPA in guinea-pigs and humans, including occupational exposure of workers, concluding that BPA is capable of producing skin sensitization responses in humans.

The Expert Meeting concurs with previous reviews that BPA is capable of producing a skin sensitization response in humans. Although studies on immune modulation are of interest, there is no clear evidence that BPA interferes with immune function.

Collectively, the available studies suggest a need to investigate BPA's ability to modulate the immune system using more standard protocols that will allow for a broader analysis of the potential adverse outcomes. However, the Expert Meeting considers this to be a low-priority research need.

7.6.2 Cardiovascular effects

None of the large-scale experimental animal studies conducted in accordance with good laboratory practice suggest effects on cardiovascular function. The limited number of specialized animal studies and in vitro assays suggest that BPA may have effects on the expression of vascular endothelial growth factor, nitric oxide synthesis and ion channels. There are no data relating these changes to downstream adverse outcomes following BPA treatment.

While very little information is available regarding the effects of BPA on cardiovascular function, the cross-sectional analyses using data from the NHANES reported associations between self-reported diagnosis of CVD and urinary BPA concentration.

In conclusion, the toxicological data do not indicate a clear effect of BPA on cardiovascular function. The Expert Meeting is aware of ongoing studies on cardiovascular function that will inform conclusions regarding cardiac end-points in the near future.

7.6.3 Metabolic disorders

There is a very large literature evaluating the effects of BPA on body weight, and surveys of these studies do not indicate that developmental exposure to BPA causes "obesity" as defined by a consistent reporting of increased body weight or growth (NTP-CERHR, 2008). This conclusion remains true when the analysis is restricted to only those studies that tested low doses of BPA, defined as less than 5000 μg/kg bw, and reported some health outcome, typically unrelated to growth and most often describing effects on reproductive tissues or neurodevelopment. Many of the studies did not detect an effect on body weight or else did not report body weight findings past the period of weaning. The magnitude of the effect in cases where an increase in body weight was observed typically ranged from 3% to 30%, with most reporting increases of 10% or less.

However, the existing studies on body weight have very limited utility for addressing the issue of adiposity, which requires internal assessments of fat mass or distribution.[1] Four studies in laboratory animals have been published since 2007 that directly address the issue of whether developmental exposure to BPA can affect adiposity, glucose or insulin regulation, lipid profiles or other end-points related to diabetes or metabolic syndrome (Miyawaki et al., 2007; Somm et al., 2009; Alonso-Magdalena et al., 2010; Ryan et al., 2010). No published studies have assessed whether BPA can cause hypertension, a risk factor for metabolic syndrome. Findings from these studies include reports of glucose intolerance and hyperinsulinaemia in the 6-month-old male offspring of OF-1 mice treated with BPA at 0.01 or 0.1 mg/kg bw per day by subcutaneous injection from gestational day (GD) 9 to GD 16 (Alonso-Magdalena et al., 2010); adipocyte hypertrophy and increased mass of parametrial white adipose and brown adipose tissue on postnatal day (PND) 21 in female offspring of Sprague-Dawley rats orally treated with BPA at 0 or approximately 0.07 mg/kg bw per day in drinking-water from GD 6 to PND 21 (Somm et al., 2009); and increased cholesterol on PND 31 in female offspring of ICR mice orally treated with BPA at approximately 0.26 or 2.60 mg/kg bw per day in drinking-water from GD 10 to weaning via the dam and then after weaning with the same drinking-water treatment as the dam (Miyawaki et al., 2007). These findings are not necessarily consistent across studies, which may be a result of variation in the dose levels tested, route of administration, strategies used to measure the end-points (i.e. fasting glucose versus glucose tolerance test) and other aspects of experimental design.

The rationale for additional research is supported by in vitro findings of effects on pancreatic function, adipocyte differentiation and adiponectin release from adipose tissue at concentrations ranging from 0.0001 to 80 μmol/l (Masuno et al., 2002, 2005; Sakurai et al., 2004; Adachi et al., 2005; Alonso-Magdalena et al., 2005, 2008; Wada et al., 2007; Hugo et al., 2008; Phrakonkham et al., 2008; Ben-Jonathan, Hugo & Brandebourg, 2009; Sargis et al., 2010) and in vivo findings of glucose intolerance and hyperinsulinaemia following acute exposures in adult mice treated with BPA at 0.01 or 0.1 mg/kg bw by subcutaneous injection (Alonso-Magdalena et al., 2006, 2008).

The two cross-sectional analyses of NHANES data that reported associations of BPA exposure with self-reported diabetes are discussed in section 6.2.4.

[1] Body weight appears to be a very crude indicator of adiposity. For example, a "thin fat" phenotype is used to describe a condition in South Asia where babies are smaller at birth but have disproportionate increases in skin fold thickness, a measure used to assess adiposity (van Steijn et al., 2009). In rodent models, there are clear examples where animals can have significant increases in adipose tissue in the absence of any difference in body weight (Ohlsson et al., 2000; Jones et al., 2001).

In conclusion, this is an emerging area of research that does not yet lend itself to reaching conclusions regarding potential risk for humans. However, the available data suggest that further assessment of the potential effects of BPA on adiposity, glucose or insulin regulation, lipids and other end-points related to diabetes or metabolic syndrome is warranted.

Additional animal studies are needed that focus on end-points related to metabolic syndrome and diabetes over a wide range of doses. The most relevant end-points include assessment of adiposity, glucose homeostasis, insulin resistance, lipid profiles and blood pressure. Studies that include developmental exposure should include assessment of effects in animals throughout adulthood, including at older ages.

The Expert Meeting was aware that some studies are already ongoing to address some of these issues.

8. Risk characterization

Risk characterization integrates the hazard identification, hazard characterization, including dose–response assessment, and exposure assessment phases of the risk assessment to determine the probability of an adverse effect occurring at current levels of exposure, with attendant uncertainties.

8.1 Exposure assessment

Oral exposure from food is generally considered the major source of BPA exposure for all age groups of non-occupationally exposed individuals. BPA concentrations in food from food surveys and BPA migration from food contact materials were considered in this assessment.

The highest estimated BPA dietary exposures were for infants 0–6 months of age who were exclusively fed with canned liquid infant formula using PC bottles. In this case, sources of BPA exposure include migration from both the formula packaging and the PC bottle. Mean exposures for infants fed with infant formula using PC bottles were 2.0–2.4 μg/kg bw per day, with 95th percentile exposures ranging from 2.7 to 4.5 μg/kg bw per day. Infants who were either fed with formula from non-PC bottles or exclusively breastfed had substantially lower estimated mean BPA exposures (0.01 μg/kg bw per day [powdered formula], 0.5 μg/kg bw per day [canned liquid formula] and 0.3 μg/kg bw per day [breast milk]), compared with those exclusively fed with infant formula using PC bottles. Once solid foods are introduced (at 6–36 months), exposure to BPA decreases relative to body weight. For children 3 years of age and older, the highest mean BPA exposure was estimated to be 0.7 μg/kg bw per day, with a maximum up to 1.9 μg/kg bw per day. Depending on the extent of packaged food (canned) in the diet, adult BPA exposures were comparable to those for children 3 years of age and older: a highest mean exposure of 1.4 μg/kg bw per day, with a maximum exposure up to 4.2 μg/kg bw per day (see Table 2 above). It was assumed that all exposure to BPA from the diet was in the form of unconjugated (aglycone) BPA, except for human breast milk. These calculated dietary exposure estimates are consistent with those obtained using data reported from available national surveys.

The toxicokinetics of orally administered BPA has been studied in rodents, non-human primates and humans. In summary, these studies have illustrated that BPA is extensively absorbed from the gastrointestinal tract, consistent with its substantial aqueous solubility and

lipophilicity. Subsequent to absorption from the gastrointestinal tract, BPA has been shown to undergo substantial presystemic Phase II metabolism in the small intestine and liver, primarily to a monoglucuronide conjugate. In primates, this major BPA metabolite is rapidly excreted in the urine, with an estimated half-life of BPA in humans of less than 2 h. This efficient first-pass metabolism limits internal exposures to aglycone BPA, and the available information on its quantitative urinary excretion in humans and non-human primates suggests that BPA does not accumulate in blood or tissues from daily dietary exposure. As a consequence, based on estimated dietary exposures, steady-state unconjugated BPA concentrations in blood are predicted by PBPK modelling to range on average from 0.04 to 10.1 pg/ml in the age group with highest dietary exposures (i.e. infants 0–6 months of age).

Based on this rapid conjugation and efficient urinary excretion, BPA exposure can be estimated using available biomonitoring data, mainly urinary BPA concentrations from spot or serial collections. Age-specific estimated 24 h urinary output volume (ml) was used to determine daily excretion of BPA, which was then presumed to be equivalent to the daily exposure, adjusted on a body weight basis (Table 3).

Table 3. Calculated exposure based on urinary BPA concentrations

Study population	Urinary concentration (µg/l)		Calculated exposure (µg/kg bw per day)		Reference for urinary concentration
	Median	95th percentile	Median	95th percentile	
1–5 months old	<0.45	10.13	0.02[a]	0.45[a]	Völkel et al. (2010)
			0.07[b]	1.61[b]	
3–5 years old	3.53	22.9	0.12	0.78	Becker et al. (2009)
6–11 years old	3.7	16.0	0.07	0.31	NHANES 2003–2004
6–60+ years old	2.7	15.9	0.05	0.27	NTP (2008)

[a] Calculation based on a urine volume of 44 ml/kg bw (see Völkel et al., 2010).
[b] Calculation based on a urine volume of 159 ml/kg bw (see Völkel et al., 2010).

In general, comparison of urine-derived daily exposure estimates, which would account for exposure to bioavailable BPA from all routes, showed good concordance with exposure estimations derived from dietary surveys. This suggests that diet is the main route of exposure to BPA.

8.2 Hazard characterization

There is an extensive literature on the evaluation of the health effects of BPA using animal models. At doses of 50 mg/kg bw per day and above, BPA has consistently been found to cause a number of adverse health effects in rodents, including fetal deaths, decreased litter size or decreased number of live pups per litter, and reduced fetal or postnatal growth in rats and mice. Typically, a dose of 5 mg/kg bw per day has been identified as a NOAEL in assessments conducted for regulatory or health-based guidance value setting purposes, based on consideration of two multigeneration studies in rats and mice conducted by Tyl et al. (2002, 2008). These studies are generally considered to be statistically and methodologically sound for the end-points investigated and have sufficient dose groups to support dose–response modelling. However, the changes in brain development, animal behaviour and prostate and mammary gland tissue, suggested in recent research reports as potential effects of exposures to BPA closer to ambient levels, were not investigated in these studies.

A number of these research reports, published in the past decade, provide some evidence for additional health effects, at considerably lower dose levels, in the range 0.002–0.2 mg/kg bw per day, particularly in studies involving exposure of animals during gestation and/or lactation. The findings reported include neural and behavioural alterations related to disruptions in normal sex differences in rats and mice and changes in prostate and mammary gland tissue, thought possibly to increase susceptibility to neoplasia later in life. The more sensitive end-points considered by the Expert Meeting as potentially relevant for hazard characterization were developmental alterations in the prostate and mammary gland in rats, altered prostate and urinary tract development in mice and early onset of puberty in female mice. In the studies in which prostate lesions in rats and altered prostate and urinary tract development in mice exposed to BPA were observed, LOAELs could be identified (minimum LOAEL = 0.010 mg/kg bw per day). The same applies to the reported lesions in the rat mammary gland, with a LOAEL of 0.0025 mg/kg bw per day. Similarly, although one study reported a LOAEL of 0.0024 mg/kg bw per day for early onset of puberty in female mice exposed to BPA, another study, using a similar experimental protocol, reported a much higher LOAEL, of 0.2 mg/kg bw per day. However, in view of the uncertainties in these data, lack of independent confirmation of the findings and lack of scientific consensus on whether the changes observed would result in impairment of functional capacity or ability to compensate for additional stresses, it is not possible to put much weight on these findings at present. In addition, elements of experimental design in these studies limit their utility in dose–response modelling (e.g. use of only one or two dose levels, non-oral route of administration and lack of data on internal dosimetry). In fact, only one study that provided evidence for effects at lower dose levels of BPA was suitable for consideration for dose–response modelling. This was a study by Jenkins et al. (2009) that reported enhanced sensitivity for developing mammary tumours in young adult female rats treated with the carcinogen, 7,12-dimethylbenz[a]anthracene (DMBA), following lactational exposure from oral treatment of the dams with BPA at 25 or 250 μg/kg bw per day. Although not measured, the lactational exposures of the pups were estimated to be two orders of magnitude lower than the administered dose to the dams (see section 4). Because of the uncertainties discussed above, however, dose–response modelling of the mammary findings in Jenkins et al. (2009) was not deemed appropriate.

There are only a few epidemiological studies in which associations between BPA exposure and human health effects have been reported, and there is considerable uncertainty in this research. There are few data on which dose–response assessment could be attempted. Two recent epidemiological studies suggesting associations between BPA exposure at ambient exposure levels with changes in a variety of sperm parameters (Meeker et al., 2010) and yield of oocytes retrieved from women undergoing in vitro fertilization treatment in fertility clinics (Mok-Lin et al., 2010) were considered by the Expert Meeting for their potential in deriving a benchmark dose. In both cases, it was concluded that in view of the cross-sectional design of these studies and lack of sufficient corroborating evidence, they indicate only an association with BPA exposure and not necessarily cause and effect. Therefore, benchmark dose modelling of these data was not undertaken.

8.3 Conclusion

Establishing a "safe" exposure level for BPA continues to be hampered by a lack of data from experimental animal studies that are suitable for risk assessment. Many research studies have design and analysis issues that limit their utility for this purpose. Controversy continues over the biological significance of many of the more sensitive end-points and whether studies that

have assessed only conventional end-points are adequate for detection of all potentially relevant effects. Continued research into the toxicokinetics of BPA and its estrogenic and other mechanisms of action will be needed before it is possible to determine the appropriate points of departure (e.g. NOAEL, LOAEL, benchmark dose) for human risk assessment with confidence.

In summary, the Expert Meeting concluded that:

- For many end-points, points of departure are much higher than human exposure. Hence, there is no health concern for these end-points.
- Studies on developmental and reproductive toxicity in which conventional end-points were evaluated have shown effects only at high doses, if at all.
- However, some emerging new end-points (sex-specific neurodevelopment, anxiety, preneoplastic changes in mammary glands and prostate in rats, impaired sperm parameters) in a few studies show associations at lower levels.
    - The points of departure for these low-dose effects are close to the estimated human exposure, so there would be potential for concern if their toxicological significance were to be confirmed.
    - However, it is difficult to interpret these findings, taking into account all available kinetic data and current understanding of classical estrogenic activity. However, new studies indicate that BPA may also act through other mechanisms.
    - There is considerable uncertainty regarding the validity and relevance of these observations. While it would be premature to conclude that these evaluations provide a realistic estimate of the human health risk, given the uncertainties, these findings should drive the direction of future research with the objective of reducing this uncertainty.

9. Alternative materials

BPA is used in the production of PC plastics and epoxy resins that come into contact with a wide variety of foodstuffs. Some alternatives to BPA-containing materials for PC bottles and containers and epoxy can linings are available on the market or proposed for use. However, at present, there appears to be no single replacement for BPA for all food contact applications. Furthermore, data on the safety of some of these replacement materials are limited or non-existent.

For PC, replacement materials include those polymers that are currently used to make bottles and containers for food packaging applications, including glass, polypropylene, polyethersulfone, polyethylene terephthalate, high-density polyethylene, PVC, polyamide and silicone. An example of a new alternative to PC is Tritan copolyester. While polyesters, polyacrylates, vinyl resins and oleoresins are available, they do not have the same performance characteristics and are not exact replacements of BPA-based epoxy resins. For example, alkyds (polyester modified with fatty acids) cannot be used for interior can coatings for beverages and food because of their susceptibility to hydrolysis and chemical attack.

It is important to note that any of these new or existing alternative materials would need to be assessed for appropriate functionality and safety using state of the art methodology and scientific knowledge.

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Annex 1

FAO/WHO Expert Meeting to Review Toxicological and Health Aspects of Bisphenol A

Ottawa, Canada, 2–5 November 2010

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Annex 2

FAO/WHO Expert Meeting on Bisphenol A

Supported by the European Food Safety Authority, Health Canada,
the National Institute of Environmental Health Sciences and
the United States Food and Drug Administration

Ottawa, Canada, 1–5 November 2010

AGENDA

1. Opening of the meeting and welcome by FAO and WHO
2. Election of the Chairperson, Vice-Chairperson and Rapporteurs
3. Adoption of the agenda
4. Declarations of interests and confidentiality agreements
5. Brief introduction and purpose of the meeting
6. Discussion on the chemistry, analytical methods, occurrence and exposure assessment
7. Discussion on toxicology and risk assessment
8. Other topics
9. Adoption of executive summary and key conclusions and recommendations

Annex 3

Report of Stakeholder Meeting on Bisphenol A

Ottawa, Canada, 1 November 2010

In order to provide an opportunity for stakeholders to present their views on the current project to review toxicological and health aspects of bisphenol A (BPA), the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) issued a public announcement of the stakeholder meeting. Persons or organizations interested in participating were asked to submit a written request, and interested parties were then invited to attend the meeting.

Eleven stakeholders made presentations; an additional three stakeholders provided written submissions only. The list of the stakeholders participating in this meeting is included at the end of this annex.

The key findings, concerns and recommendations presented by the stakeholders, as compiled below, were provided to the Expert Meeting to be considered in their discussions. It is emphasized that these are solely the views presented by stakeholders at the meeting and do not represent the views of any of the organizing or supporting organizations.

Analytical methods for detection in food

- Cross-contamination during packaging, manufacturing, storage or shipment can result in detectable levels of BPA, even when no BPA is intentionally used; and during analysis, even in tightly controlled laboratory settings
- Need a validated, harmonized analytical methodology that has adequate accuracy, precision, reproducibility, specificity and sensitivity to determine compliance with established regulatory limits
- Analytical methods need to determine concentration of BPA that has migrated into food, not concentration in packaging
- Methods must be fit for purpose, specific to type of sample being tested
- Expert panel encouraged to consider establishing universal validated testing method for BPA in infant formula

Occurrence of BPA in the diet, including studies on migration of BPA from food contact material

- Need to conduct studies on the leaching of BPA from polycarbonate feeding utensils under conditions of sterilization (e.g. boiling water or storage in sterilizing solution), when mixing water with powdered formula at 70 °C, and when using microwave ovens to heat or sterilize feeding equipment

Toxicity of BPA based on laboratory animal studies

- Many low-dose exposure studies are not suitable for use in risk assessment, and scientific uncertainties in these studies need to be addressed by additional research
- In particular, studies conducted on developing animals have many methodological shortcomings, such that the relevance of the findings for human health cannot be assessed

- Extrapolation of data between experimental animals and humans is highly uncertain; key differences in bioavailability and half-lives in rats, for example, mean that effects reported in early postnatal rats likely overpredict effects in primates of the same age
- Studies by the oral route are the only applicable ones due to route differences in kinetics, for example

Epidemiological studies

- Current epidemiological studies are cross-sectional in design and not suitable for risk assessment purposes, particularly because of the short half-life of BPA and the potential for health effects that occur over longer periods of time

Exposure assessments of BPA from dietary sources

- Urinalysis data are the most reliable, robust and consistent data for the evaluation of total human exposure to BPA by all sources and routes
- Due to extensive first-pass metabolism, internal concentrations of BPA are at least in the range of 100-fold lower than concentrations of BPA-glucuronide; in other words, there is negligible bioavailability of BPA after oral exposure
- Blood biomonitoring provides questionable data that are inconsistent with estimates from food consumption and urine biomonitoring and likely do not accurately reflect BPA bioavailability in humans
- Future blood biomonitoring studies should use analytical methods that are carefully validated to demonstrate the absence of significant levels of BPA contamination and that measure both parent and conjugated BPA to demonstrate that any parent BPA detected is internally consistent with the level of conjugated BPA
- Need more data on non-oral exposure (e.g. dermal exposure through cash register receipts)
- Expert panel should clearly define the meaningful measure of BPA exposure as the concentration of BPA in food in its ready to consume form

Human health risk assessments of BPA, including consideration of sensitive subpopulations and sensitive life stages

- Need to define realistic potency relationships between BPA and other estrogenic substances, including estradiol
- Expert panel is encouraged to consider establishing a uniform safe level of BPA in infant formula
- Need to weigh potential effects from BPA in epoxy coatings in metal packaging against the health benefits from reduction of serious effects of foodborne illness

Alternatives/replacements currently used, or proposed for use, and their potential risks to human health

- There is no readily available, suitable alternative that meets the essential safety and performance requirements for the broad spectrum of all foods now packaged in metal containers
- All alternative coatings need to be thoroughly evaluated for performance for the full shelf life of the product and for safety, as the potential toxicity of alternatives is a major concern; they may require modification of production lines; they also need regulatory review prior to introduction to the marketplace: it could take up to seven years for the introduction of an alternative coating to the marketplace
- Alternatives to BPA baby bottles include stainless steel bottles and breastfeeding

Risk communication

- Media needs to base communication on fact; lack of balanced, science-based information impacts overall consumer perceptions and attitudes, especially in areas of growing concern
- Consensus science should be communicated properly and effectively to inform the decision-making process
- Industry needs to be more transparent in communicating with the public

List of Stakeholders[1]

1. **Catherine Abel**,* Food & Consumer Products of Canada, Toronto, Canada
2. **Marie-Hélène Bani-Estivals**, European Federation of Bottled Water, Brussels, Belgium
3. **Mark Beazley**, Retail Council of Canada, Toronto, Canada
4. **Melanie Budicky**, McCain Foods Canada, Toronto, Canada
5. **Kathleen Cooper**,* Canadian Environmental Law Association, Toronto, Canada
6. **Jackie Crichton**, Canadian Council of Grocery Distributors, Pakenham, Canada
7. **Loretta Del Bosco**, Abbott Laboratories, St-Laurent, Canada
8. **Sara Edge**, McMaster Institute of Environment & Health, Hamilton, Canada
9. **Anthony Flood**,* International Food Information Council, Washington, USA
10. **Elizabeth Griswold**, Canadian Bottled Water Association, Richmond Hill, Canada
11. **Lois Haighton**,* Cantox Health Services International, Mississauga, Canada
12. **Luke Harford**, Brewers Association of Canada, Ottawa, Canada
13. **Steven G. Hentges**,* American Chemistry Council, Washington, USA
14. **Robert R. Hirst**, International Bottled Water Association, Alexandria, USA
15. **Dale R. Johnson**, Abbott Laboratories, Abbott Park, USA
16. **Daniel L'Heureux**, Crown Cork & Seal, Dorval, Canada
17. **Bidemi Odeyemi**, Ecologo, Ottawa, Canada
18. **Nancy J. Rachman**,* Grocery Manufacturers Association, Washington, USA
19. **Robert Rankin**,* International Formula Council, on behalf of International Special Dietary Foods Industries, Washington, USA
20. **John Rost**,* North American Metal Packaging Alliance Inc., Washington, USA
21. **C. Tom Seipelt**,* Abbott Laboratories, Columbus, USA

[1] Stakeholders who gave oral presentations are marked with an asterisk (*). Written submissions were also provided by the Can Manufacturers Institute, Washington, DC, USA; the International Baby Food Action Network (IBFAN), Geneva, Switzerland; and James Gomes, Faculty of Health Services, University of Ottawa, Ottawa, Canada.

22. **Rick Smith**, Environmental Defence, Toronto, Canada

23. **John M. Waechter**,* The Dow Chemical Company, Midland, USA

24. **Jane Walter**,* OrganicKidz, Calgary, Canada

25. **Patti Wunsch**, Agriculture & Agri-Food Canada, Ottawa, Canada