ALTERNATIVES ANALYSIS REPORT FOR BISPHENOL-A IN INFANT FORMULA CANS AND BABY FOOD JAR LIDS

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TABLE OF CONTENTS

FIGURES

TABLES

APPENDICES

CHEMICAL ALTERNATIVES ASSESSMENT FOR BISPHENOL-A IN INFANT FORMULA CANS AND BABY FOOD JAR LIDS

1.0 Introduction and Background

Food jars and cans must protect their contents, often under severe conditions. They must maintain an airtight seal even under pressure, and prevent changes to food taste, odor, appearance and texture. The best possible containers are interchangeable to meet the needs of multiple food manufacturers. They must be resistant to damage during handling, cost competitive and have minimal environmental and human heath impacts.

Bisphenol A (BPA)-based materials are pervasive in the U.S. economy (USEPA 2010). BPA is a high production volume (HPV) chemical widely used in manufacturing polycarbonate (PC) plastics and epoxy resins, including those commonly found in infant formula cans, baby bottles and baby food jar lids. Research has shown that BPA is a hormone-disrupting chemical found in the urine of nearly all individuals tested by the Centers for Disease Control and Prevention (CDC) and the National Health and Nutrition Examination Survey, indicating widespread exposure to BPA in the United States population (Calafat et al, 2008). Exposure to BPA occurs when BPA leaches into food or beverage products and is subsequently ingested by the individual. BPA leaches into food and beverage products when the BPA-containing-packaging is heated, either during the manufacturing process (e.g., formula preparation, canning process) or in the home directly by individuals. Exposure to BPA may also occur from dental treatments (e.g., dental sealants, composite fillings), handling of cash register receipts (i.e., thermal printer paper) and numerous other sources. However, the focus of this assessment is exposure to BPA from infant formula cans and baby food jar lids.

The US Food and Drug Administration (FDA) has indicated that it supports the replacement of BPA in food containers where the replacement constituent is sufficiently protective of food safety and quality (USFDA, 2010a).

The US Environmental Protection Agency (EPA) Design for the Environment (DfE) provides a process to evaluate chemical alternatives, considering product manufacture, use, disposal, and functionality, while placing a premium on protection of public health (Lavoie et al, 2010). Aside from the protection of human health, viable alternatives must be evaluated on their cost and performance, including their commercial availability and technical feasibility for implementation. The DfE utilizes a hazard-based assessment – one that doesn't hinge on exposure. The Clean Production Action (CPA) GreenScreen process specified for use in Maine's *Regulation of Chemical Use in Children's Products,* 06-096 CMR 880(3)(B)(3)(e) also identifies all relevant health considerations, without limitation as to dose – as it applies to a pragmatic assessment of expected human exposures. Both approaches fall short of an assessment which considers the amount of constituent (dose) which is absorbed (or administered) over a defined period of exposure, given use of a particular product stream.

Alternatives to BPA-containing packaging fall into two basic categories: 1) alternative plastics and 2) non-plastic alternatives. This assessment attempts to focus on alternative plastics, but identification of a drop-in replacement for BPA is unlikely at this time, considering the degree of scrutiny this chemical has been subjected to over the last decade. A replacement polymer with

the same functionality as BPA has not been identified. Non-plastic alternatives include glass, aseptic cartons and foil pouches.

The purpose of this Alternatives Analysis Report (AAR) is to provide private industry and the State of Maine with a defensible framework and example document detailing the AAR process, focusing on BPA in infant formula cans and baby food jar lids. The Maine Department of Environmental Protection (DEP) seeks to create a final report that meets all of the requirements in the Code of Maine Rules (CMR) (referenced below) and aims to investigate the currently available and emerging alternatives.

The prescribed requirements for an AAR are detailed in *Regulation of Chemical Use in Children's Products,* 06-096 CMR 880(3)(B)(3) and are listed below:

> (a) Describe the function of the priority chemical in the product and list the specific characteristics of the chemical (e.g., physical or chemical properties; price; availability) that led to its selection to fulfill that function;
>
> (b) Identify the specific chemical and non-chemical alternatives considered in lieu of the priority chemical, and describe why the priority chemical was selected over each identified alternatives;
>
> (c) Identify and describe any known emerging chemical and non-chemical alternatives to use of the priority chemical in the product and, for each such alternative, provides the following information:
>
> (i) The status of research and development;
> (ii) The current barriers to introduction of the alternative into the marketplace;
> (iii) The projected timeframe for introduction of the alternative into the marketplace; and
> (iv) The advantages and disadvantages of using the alternative in lieu of the priority chemical, assuming the alternative is successfully introduced into the marketplace;
>
> (d) Identify the key, distinguishing human health and environmental hazards (or "endpoints") associated with the priority chemical;
>
> (e) Evaluate the human health and environmental hazard posed by the priority chemical and each identified chemical alternative using the Green Screen or other evaluation methodology approved by the department; and;
>
> (f) Provide copies of all peer-reviewed studies or government-generated studies identified through a search of publicly accessible databases and lists the search terms used. The search must be conducted for the priority chemical and for each chemical alternative identified pursuant to subparagraph (b) and (c) and must, at a minimum, include as search terms the endpoints identified pursuant to subparagraph (d).

In providing a defensible framework and example AAR process which meets the requirements of Maine's regulation, this AAR is organized to first present the state of science of BPA, including the basis for concern, followed by a discussion of the status of research and development, the functionality and the advantages and disadvantages of the

various BPA alternatives. Where relevant, patent references are included for alternatives with less than a widespread presence in the packaging market. Included in the comparison of the functionality of these alternatives is a summary of the human health and environmental evaluations. Tables are provided to support the text discussions and Appendices are provided to include supplemental information such as an End of Life Evaluation regarding the recyclability of the various alternatives and the GreenScreen report performed for BPA. Research and preparation of this AAR involved searches of primary literature sources (e.g., United States National Library of Medicine Databases, EBSCO Publishing Database which searches numerous journals), direct communication with manufacturing company representatives, review of agency scientific publications (e.g., US Food and Drug Administration, US Environmental Protection Agency), review of the Clean Production Action (CPA) List of Lists (referred to as the "Red List"), and review of the State of Maine Chemicals of Concern.

2.0 State of Science of BPA

The health implications associated with BPA exposure addressed in the following sections, and in the attached GreenScreen report, discuss any and all potentially adverse health effects associated with BPA via any investigated and documented route of exposure as reported in peer-reviewed journal articles or published administrative authority position or guidance document. The discussion of associated health effects is not limited to a particular dose range, constituent delivery mechanism, or receptor population. Because the focus of this Alternative Analysis is on infant formula and baby foodstuffs, a targeted human health assessment, focused on dose and route of exposure is the more appropriate metric to underpin administrative authority decisions limited to actual or expected health risk for the targeted populations. Utilization of USEPA's Integrated Risk Information System (IRIS)-promulgated oral reference dose (RfD_o), could underpin an exposure assessment specific to nursing infants and babies predicated on ingestion of BPA-contaminated food. Development of a Human Health Risk Assessment for BPA exposure to nursing infants and babies is beyond the scope of this assessment.

2.1 Chemical Characteristics and Function of BPA

Chemical at Issue

BPA (Chemical Abstracts Service [CAS] number 80-05-7) is manufactured by condensation of 2 mol phenol with 1 mol acetone in the presence of an acid catalyst such as hydrogen chloride (O'Neil 2006, Ullmann 2003). The molecular formula for BPA is $C_{15}H_{16}O_2$ and the 2-dimensional and 3-dimensional structures are shown in Figures 1 and 2.

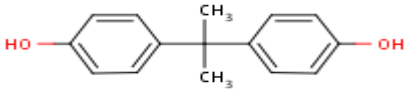

Figure 1. 2D Structure (NLM TOXNET 2012)

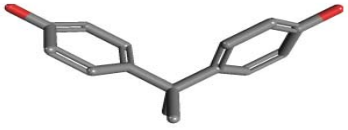

Figure 2. 3D Conformer (PubChem 2012)

The physical properties of BPA are summarized in Table 2-1.

Table 2-1: Chemical/Physical Properties of BPA

Parameter	Value/Description	Source
Molecular Weight	228.29 g/mol	O'Neil 2006
Boiling Point	220 deg C at 4 mm Hg	O'Neil 2006
Melting Point	150-155 deg C (solidification range)	O'Neil 2006
Density/Specific Gravity	1.195 at 25 deg C/25 deg C	Lewis 2001
Octanol/Water Partition Coefficient	log Kow = 3.32	Hansch et al. 1995
Water Solubility	120 mg/L at 25 deg C	Dorn PB et al. 1987
Vapor Pressure	$3.91x10^{-7}$ mm Hg at 25 deg C	USEPA 2004
Henry's Law Constant	$1.0x10^{-11}$ atm-cu m/mol at 25 deg C	USEPA 2004
Color/Form	White crystals or flakes	O'Neil 2006
Odor	Mild phenolic odor	O'Neil 2006

Functionality and Desirable Characteristics

BPA is manufactured primarily for use in making PC plastic. PC plastic is a high-performance, strong, durable, light material that is a key component in many everyday items. Another common use of BPA is in the manufacture of epoxy resins. Epoxy resins are used to make protective coatings (also referred to as can lining or can liners) on metal food and beverage containers including infant formula cans and baby food jar lids.

The purpose and function of a protective coating is to preserve the integrity and safety of canned food by preventing corrosion and contamination. Most steel cans utilize a tin coating to allow targeted oxidation of the tin, rather than degradation of the food to help protect the integrity of products. In cans without organic lining, tin dissolution provides protection of the steel iron component (Coles and Kirwin, 2011). Tin corrosion can allow direct contact of the product with the steel of the can proper, leading to increased internal pressure and a reduction in can integrity. In aluminum cans, an oxide coating naturally forms with exposure to ambient air or water Oldring and Nehring, 2007). This coating is resistant to chemical dissolution, but it is susceptible to high and low pH conditions. In the absence of a durable organic coating, aluminum can shelf life is inadequate to serve the marketplace. Typical organic coatings which are commercially available include oleoresins (implemented decades ago, and in wide use prior to 1965, but susceptible to corrosion based on their open micellular structure). Oleoresins were largely abandoned with the implementation of BPA in the marketplace. Synthetic resins include acrylics, epoxies, phenolics, polyesters and vinyl resins.

BPA can linings were widely implemented because they were shown to be effective not only in extending the shelf life of canned goods, but also in preventing potentially fatal bacterial contamination. BPA-lined cans ensure that highly acidic foods will not allow heavy metals to leach from cans into the food itself. Also, the lining acts as an additional layer in the sealing process and helps prevent food spoilage and botulism, a rare but serious paralytic illness caused by a nerve toxin that is produced by the bacterium *Clostridium botulinum* and sometimes by

strains of *Clostridium butyricum* and *Clostridium baratii* (CDC 2010).[1] Botulism can be fatal and is considered a medical emergency (CDC 2010). In addition, BPA linings are colorless, tasteless and odorless and do not negatively affect the aesthetic quality of the product, while also being out of patent and thus relatively inexpensive to produce. These beneficial capabilities of BPA—when combined with its high-performance characteristics of toughness, adhesion, formability, chemical resistance, optical clarity, high heat resistance and excellent electrical resistance (USEPA 2010)—made BPA a popular choice for can linings.

2.2 Rationale for Selection of BPA in lieu of Alternatives

Selection of BPA products in lieu of suitable alternatives is manufacturer-specific. As noted previously, BPA-based materials are largely chosen for their high performance characteristics though another driving force is that BPA is inexpensive to manufacture making it suitable for mass production (Pierce and Caliendo, July 2012). Alternatives evaluated in this assessment are described in Section 3.0 and specific barriers to entry into the market place are noted in Section 3.3 where applicable.

2.3 Key Human Health and Environmental Hazards Associated with BPA

2.3.1 Human Health Hazards

BPA is widely regarded as an endocrine disruptor, which USEPA defines as "an exogenous chemical substance or mixture that alters the structure or function(s) of the endocrine system and causes adverse effects" in individuals, their offspring or populations. Hormones have many modes of action, including the ability to initiate or suppress gene transcription. Endocrine disruptors interfere with those genetic-level processes. The timing of exposure is critical because vulnerability changes over a lifespan. In an adult, where sex-specific physiology and behaviors have matured and function properly, interference with hormone action is likely reversible once exposure ends. This is not thought to be the case in the developing fetus or infant. Therefore, fetuses and infants are the groups most at risk for adverse effects from an endocrine disruptor such as BPA.

Infant dietary exposure is the primary focus of this AAR. Infants may be exposed to BPA by ingesting formula from BPA-lined cans or baby food packaged in glass jars with BPA-lined lids (National Toxicology Program 2010, McNeal et al. 2000). BPA leaches into food products when the BPA-containing-packaging is heated, either during the manufacturing process (e.g., formula preparation, canning process) or in the home

[1] Infant botulism is caused by consuming the spores of the botulinum bacteria, which then grow in the intestines and release toxin (CDC 2010). In the United States, an average of 145 cases are reported each year and approximately 15% involve foodborne botulism and 65% involve infant botulism (CDC 2010). The primary dietary cause of botulism in infants relates to honey ingestion within the first year of life; however, other sources are possible (CDC 2010). Infants with botulism appear lethargic, feed poorly, are constipated, and have a weak cry and poor muscle tone, which are symptoms of the muscle paralysis caused by the bacterial toxin. If untreated, these symptoms may progress to cause paralysis of the respiratory muscles, arms, legs, and trunk, and can be fatal (CDC 2010). Conduct of a human health evaluation of can coatings is extremely difficult, not only because many of the coatings currently utilized in the marketplace are considered proprietary by the manufacturers, and consequently gathering information about the relative concentrations or the actual nature of additives is problematic, but also because of the varied types of monomers, polymers and copolymers available for combination in the market. Organic coatings comprise a formulation inclusive of the base product, but many additional plasticizers, antioxidants, catalysts, stabilizers, hardeners, pigments and other additives complicate even a generic assessment predicated on the "expected" formulations. These cannot be known in the absence of full disclosure by the producer. For example, the North America Metal Packaging Alliance lists over 1,700 can coating specifications.

directly by individuals. Studies show BPA is present in canned infant formula and baby food (McNeal et al. 2000). For example, McNeal et al. (2000) found BPA concentrations in canned infant formula ranging from 0.1 to 13.2 ng/mL.

Many of the studies reviewed in preparation of this report address exposures, which are not directly pertinent in an assessment of nursing infants and babies ingesting baby food. For example, many of the studies reviewed target *in utero* or adult occupational exposure. The primary concerns associated with BPA exposure for nursing infants and babies relate to the potential for this compound to elicit developmental or behavioral effects with a lessened degree of concern regarding an acceleration in the onset of puberty.

BPA is a reproductive and developmental toxicant at doses in animal studies of ≥ 50 mg/kg-bw/day (delayed puberty in male and female rats and male mice); ≥ 235 mg/kg-bw/day (reduced fetal or birth weight or growth early in life, effects on testis of male rats); and ≥ 500 mg/kg-bw/day (possible decreased fertility in mice, altered estrous cycling in female rats, and reduced survival of fetuses). Systemic effects such as a reduction in body weight, changes in relative organ weights, and increases in liver toxicity were observed at doses above 5 mg/kg-bw/day (identified as a No-Observed-Adverse-Effect-Level [NOAEL] with a Low-Observed-Adverse-Effect-Level [LOAEL] of 50 mg/kg-bw-day) (USEPA 2010). The current USEPA oral reference dose for BPA for use in assessing human exposure is 5E-02 mg/kg-day, from EPA's Integrated Risk Information System (IRIS). Low-dose effects relate to endocrine disruption and include effects on puberty and developmental neurotoxicological effects on the brain and behavior at doses as low as 2 ug/kg-bw/day in animal studies (USEPA 2010).

Recent studies by the US Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) indicate that the latest estimate of average dietary exposure, based on increased data collection, is 0.2-0.4 ug/kg-bw/day for infants and 0.1-0.2 ug/kg-bw/day for children and adults (USDHHS 2012). Geens et al, (2012), indicates that the 95th percentile of ingestion rate for infants (based on urinary excretion studies in US populations) may be as high as 1.61 ug/kg-day. However, there is lack of consensus about impacts to human health, even at very low-dose exposure.

Most studies of the health effects of BPA have focused on estrogenic activity because it is widely documented to function as an agonist of certain estrogen receptors (Lee et al. 2003), and as an androgen antagonist and to suppress aromatase activity (Bonefeld-Jorgensen et al. 2007) (Melzer et al. 2011). Thyroid hormone disruption (Moriyama et al. 2002), altered pancreatic β-cell function (Ropero et al. 2008), and obesity-promoting effects (Newbold et al. 2008), have also been reported in research studies. Many of these effects are already detectable at intakes less than the current tolerable daily intake (TDI) of 0.05 mg/kg/day, prompting concerns that the TDI should be revised (Melzer et al. 2011). However, there has not been a strong body of evidence that BPA at these low levels exerts significant and substantive biological effects in humans until recently. Melzer et al. (2011) found that BPA exposure is associated with *in vivo* estrogenic gene expression in adults and is associated with male infertility. Also, research performed by Braun et al. (2009) found an association between mean prenatal BPA concentrations and externalizing scores in females. Higher prenatal BPA concentrations to female fetuses at 16 weeks gestation also correlated with higher externalizing scores. Further, Rissman et

al. (2012) found that low dose gestational exposure to BPA, a dose within the reported human levels, leads to trans-generational behavioral changes in mice, including increased anxiety, aggression and cognitive impairments for four generations (The Endocrine Society News Room 2012). The study by Wolstenholme et al., *Gestational exposure to Bisphenol A produces trans-generational changes in behaviors and gene expression,* appeared online June 15, 2012 at: http://endo.endojournals.org/content/early/2012/06/15/en.2012-1195.abstract..

Listed below is a synopsis of recent health effects documented in primary literature sources and excerpted from *An Update on the Recently Published Peer-Reviewed Scientific Literature on Bisphenol A (BPA)* (Vandenberg, 2012a):

- A 2009 study reported that prenatal exposure to females was associated with an increase in hyperactivity and aggression in 2-year-old girls (Braun et al., 2009). In a follow-up assessment of this cohort of children, average maternal BPA levels were associated with an increase in anxiety and hyperactivity, and poorer emotional control and inhibition in 3-year-old girls (Braun et al., 2011b). These results suggest that the behavior of BPA-exposed girls was masculinized. This developmental behavior result has been recorded in animal studies, which have indicated that BPA can masculinize behaviors of female rodents, and may feminize the behaviors of male rodents (Adewale et al., 2011; Patisaul et al., 2006; Patisaul et al., 2009; Rubin et al., 2006).

- Maternal BPA exposures may be associated with an increase in premature births (Cantonwine et al., 2010; Chou et al., 2011; Miao et al., 2011b). Maternal exposure to BPA during pregnancy was also associated with decreased anogenital distance in males (Miao et al., 2011a), suggesting feminization of male offspring. Maternal BPA levels also influenced newborn hormone levels that are associated with lipid metabolism (Chou et al., 2011). These results are consistent with a study in mice documenting disruption of glucose homeostasis in mothers and their male offspring as a function of increased BPA exposure (Alonso-Magdalena et al., 2010b). Offspring may therefore be at risk for diabetes or obesity later in life.

- BPA exposure may also influence the developing immune system. Prenatal exposure at 16 weeks gestation, but not later prenatal exposure at 26 weeks gestation or neonatal exposure, was associated with an increase in child wheeze at six months of age (Spanier et al., 2012). Additionally, BPA levels were associated with antibody titers to a common pathogen (cytomegalovirus, viral infection of the esophagus), although the relationship was reversed for individuals younger vs. older than 18 years old (Clayton et al., 2011).

- Increased BPA levels are associated with decreased sperm quality following environmental (Meeker et al., 2010b) and occupational (Li et al., 2011) exposure. Higher BPA levels were also associated with poorer sexual function in occupationally or environmentally exposed men, including decreased sexual desire and decreased erection and orgasmic function (Li et al., 2010a; Li et al., 2010b). Several studies indicate that environmental exposures to BPA affect testosterone levels in men (Galloway et al., 2010; Meeker, 2010; Mendiola et al., 2010), and are

associated with changes in estrogenic gene expression in adult males (Melzer et al., 2011). In women receiving *in vitro* fertilization, higher BPA concentrations were associated with poorer oocyte quality, decreased estradiol levels, and decreased implantation success (Bloom et al., 2011; Ehrlich et al., 2012; Fujimoto et al., 2011; Mok-Lin et al., 2010).

- In 2008, the first study showing an association between urinary BPA levels and heart disease was published: individuals with higher BPA levels were more likely to report cardiovascular diseases (Lang et al., 2008). In 2010, another cross-sectional study representative of the US population found that higher BPA levels were associated with an increased incidence of coronary heart disease (Melzer et al., 2010). This study was followed by a longitudinal study, in which BPA exposures were measured in adults free of coronary heart disease, and these individuals were then followed for 10.8 years (Melzer et al., 2012). Individuals with higher urinary BPA levels at time zero were more likely to develop coronary heart disease at the end of the study compared to individuals with low urinary BPA concentrations at time zero. This study thus addresses the issue of causation, and suggests that BPA exposures could cause heart disease (and refutes the suggestion that heart disease causes increases in BPA exposure).

- BPA activates the human pregnane X receptor (Sui et al., 2012), which is involved in lipid homeostasis, in addition to steroid and xenobiotic chemical metabolism. BPA may affect other endocrine parameters in addition to reproductive hormones and possibly metabolic homeostasis. Specifically, higher BPA levels were associated with decreased thyroid hormone levels in adults (Meeker et al., 2010a; Meeker and Ferguson, 2011).

- There is considerable evidence that BPA interferes with male and female reproduction, brain development, the adult brain, metabolic processes, and development of the mammary gland (Vandenberg et al., 2012b). Various associated effects in numerous studies were observed at blood levels consistent with levels in humans in the general population (Vandenberg et al., 2007; vom Saal et al., 2007).

  Table 2-2 presents a summary of BPA intake limits for human health assessments. Intake limits are provided from various national and international sources, and were derived as part of animal dose response studies. Assessment endpoints are provided for each intake limit. Intake limits are provided in milligram per kilogram per day (mg/kg/day), and thus correspond to a daily maximum intake corresponding to the endpoint (e.g., target organ or response such as reduced body weight, irreversible reproductive effects, reversible reproductive effects and other endpoints).

Table 2-2: BPA Intake Limits for Human Health Assessments (USEPA 2010)

Authors	Intake Limit (mg/kg/day)[1]	Endpoint (Animal dose in mg/kg/day) and Source
USEPA's Integrated Risk Information System (IRIS) (1993)	0.05	Reduced body weight (5) NTP 1982 two-year cancer study in rats and mice (as cited in USEPA, 1993)
FDA (2008)	0.005	Systemic – reduced body wt and liver effects (5)
	0.05	Irreversible reproductive effects (50)
	0.5	Reversible reproductive effects (50) (All based on both 2-generation mouse study (Tyl et al., 2008) and 3-generation rat study (Tyl et al., 2002)
European Food and Safety Authority (EFSA) (2006, 2008a-b)	0.05	Used 5 (lowest value in cited studies) Tyl et al. (2002, 2008)
Japan (AIST, 2007)	0.05	Body weight (5) Tyl et al. (2002, 2008)
	0.5	Reproduction (50) Tyl et al. (2002, 2008)
Canada (2008)	Not reported	Body weight reduction (5) and developmental and reproductive effects (50), Tyl et al. (2002, 2008) Cited numerous studies with effect levels ranging from 0.010 to 0.100 mg/kg/day for a variety of effects in mice and/or rats including changes in: maternal behavior, gender-specific behaviors; sexual performance; novelty-seeking/impulse behaviors; avoidance response; maze performance.
Willhite et al. (2008) (NSF International)	0.016	Used 5 (lowest value in cited studies) Tyl et al. (2002, 2008)

[1] Most risk assessments take an exposure value from an animal study (dose in mg/kg-bw/day) and divide it by several uncertainty factors to arrive at an acceptable dose in humans. This value is what is shown here as an "intake limit" and is what is compared to an expected/estimated exposure value in a risk assessment. The uncertainty factors used by the various assessments are: EPA (IRIS) – 1000; FDA – either 1000 (systemic or irreversible effects) or 100 (reversible effects); EFSA/EU – 100; Japan – either 100 or 500; Canada – did not specify; and NSF Int.'l – 300.

2.3.2 Environmental Hazards

BPA surface water concentrations have been measured in samples collected from rivers, estuaries, and canals around the world. Maximum concentrations of BPA typically fall well below 1 µg/L (with most concentrations below 0.1 µg/L), even though a few of the reported concentrations range between 1 and 20 µg/L. Higher concentrations (0.5 µg/L to > 1 mg/L) of BPA have been reported in undiluted landfill leachates and sewage post-treatment effluents. BPA is rapidly degraded in the environment via microbial- and photodegradation, and is therefore not expected to persist in the environment. The compound also has a low potential to bioaccumulate in animals (Crain et al., 2007).

Crain et al. (2007) reviewed the published literature on the effects of BPA to aquatic invertebrates, fish, amphibians, birds, and mammals. The available evidence showed that exposure to BPA induces feminization during gonadal development in fish, reptiles, and birds, but only at concentrations not observed in the environment. On the other hand, exposure by adult fish to environmentally-realistic concentrations of BPA (i.e., 1.0 to 20 µg/L) in surface water can impact spermatogenesis, cause intersex, and stimulate vittalogenin synthesis in livers (a sign of feminization). Several studies reported skewed sex ratios in larval stages of the clawed frog (*Xenopus laevis*) exposed to the same range of BPA concentrations (i.e., 1.0 to 20 µg/L). Two invertebrate species (the harpacticoid copepod, *Tigriopus japonicas*, and the ramshorn snail, *Marisa cornuarietis*) showed developmental delays and increased egg production, respectively, when chronically exposed to BPA at concentrations ranging from 0.1 to 1.0 µg/L.

The European Union (EU), Canada, and Japan reviewed the scientific literature on the effects of BPA on aquatic receptors to derive Predicted No Effect Concentrations (PNECs, which are equivalent to No Observed Effect Concentrations or NOECs). The EU and Japan used different data sets and calculation methods, but generated similar PNECs of 1.5 µg/L and 1.6 µg/L, respectively (see Table 4.2 for details). At the time of report production, PNECs are not published or documented from the US.

Canada used a more conservative assessment. It derived a PNEC based on a study which assessed semen quality and ovulation timing in brown trout exposed to BPA in surface water at concentrations ranging between 1.75 and 5.0 µg/L. The lowest test concentration (1.75 µg/L) affected sperm density and motility and also delayed spawning by four weeks. This lowest observed effect concentration was then divided by an uncertainty factor of 10 in order to derive a conservative PNEC of 0.175 µg/L. This value falls well within the range of environmentally-realistic BPA concentrations measured in surface water samples. Canada stated in its hazard characterization of BPA that (see p. 19 of the report), "[C]onsidered together, the data provide strong evidence that bisphenol A is capable of eliciting adverse effects: (1) following prolonged exposures at levels below those usually seen to elicit effects in standard toxicity tests (i.e., tests based on recognized methods which evaluate endpoints such as survival, reproduction, and growth); (2) following brief low-dose exposure, particularly at sensitive developmental stages, with

effects apparent later in the life cycle; (3) on filial generations following parental exposure; and (4) using more than one mode of action (Canada, 2008).

Table 2-3 presents a summary and comparison of the PNECs established by the EU, Canada and Japan. The table summarizes the different approaches for generating PNECs. A PNEC is compared directly with an exposure value to evaluate risk, and if the ratio of the exposure point concentration to the PNEC is less than one, then the risk is generally deemed acceptable.

Table 2-3: Summary of Bisphenol A Ecological Hazard Values (USEPA 2010)

Country	**Predicted No Effect Concentrations**	**Endpoint and Source**
European Union (EU)	1.5	The predicted no effect concentration (PNEC) for aquatic organisms derived by using a statistical analysis of data from available data on freshwater and marine aquatic organisms (in this case, 16 different studies, unpublished and published, from 10 different taxonomic groups) to arrive at a value of 7.5 µg/L, which is divided by an uncertainty factor of 5, resulting in a PNEC of 1.5 µg/L (EU, 2008).
Canada	0.175	This PNEC was derived by using a lowest observed effect concentration (LOEC) of 1.75 µg/L for reduced semen quality and delayed ovulation in a published brown trout study (Lahnsteiner et al, 2005) and applying an uncertainty factor of 10 (Canada, 2008).
Japan	1.6	The PNEC was derived by using the 16 µg/L no effect concentration (NOEC) for egg hatchability in fathead minnows from the unpublished 3 generation study by Sumpter, et al. (2001) multigeneration fish study and dividing by an uncertainty factor of 10 (AIST, 2007).

[1] In Europe, Canada, and Japan, a predicted no effect concentration (PNEC) is compared directly with an exposure value to evaluate risk. If the ratio of environmental concentration to PNEC is less than one, the risk is generally considered acceptable. As noted in the table, countries use different approaches for generating PNECs, and the precise values may differ even when based on the same studies.

3.0 Description of Petroleum Based Chemical Polymers and other Renewable/Composite Material Packaging Alternatives to BPA

3.1 Liquid Infant Formula Packaging Alternatives

Alternatives considered in lieu of infant formula cans lined with BPA coating include liquid formula packaged in plastic bottles such as Polypropylene (PP), Polyethylene (both in Low Density (LDPE) and High Density (HDPE)), Polyethylene terephthalate (PET or PETE), Tritan Copolyester™ and Polystyrene (PS).

Cans with polyester coatings (e.g., DAREX Polyester), PET film, baked-on resins (e.g., Oleoresin), or corn-based isosorbide diglycidyl ether liners (under patent, developed by New Jersey Institute of Technology [NJIT]) are additional alternatives to BPA-lined cans.

3.2 Baby Food Packaging Alternatives

Based on a review of alternatives, glass jars could also have lids lined with polyester coatings (e.g., DAREX Polyester), PET film, baked-on resins (e.g., Oleoresin), or corn-based isosorbide diglycidyl ether liners.

Similarly, BPA alternatives considered in lieu of baby food in glass jars with BPA-lined lids include baby food packaged in plastic bottles such as PP, PET, HDPE, PS and Polylactic Acid (PLA).

Aseptic containers, as well as laminated pouches, with PE as the food contact surface could also be suitable options.

Table 3-1, at the end of this section, summarizes the considered and preferred alternatives and provides the status of research and development, the current barriers to entry into the marketplace, the projected timeframe for introduction of the alternatives into the marketplace, and some advantages and disadvantages of using the alternatives in lieu of packaging inclusive of BPA. Table 3-2 provides a comparison of the advantages and disadvantages of the functionality of BPA alternatives.

3.3 Status of Research and Development and Barriers to Entry

This section provides an alternative-specific discussion regarding the status of research and development for various BPA alternatives. Barriers to entry into the market place are noted where applicable.

3.3.1 Polypropylene (PP) Containers

PP containers are currently and readily available in the marketplace, and are classified as #5 plastic. There are no associated barriers to entry. PP containers are currently used to package infant formula (e.g., Abbott) and baby food (e.g., Danone's YoBaby)

3.3.2 Polyethylene (PE) Containers

PE containers consist of LDPE, HDPE, PET and PETE containers. PE containers are readily available in the marketplace; PE is a component of #1, #2, and #3 plastics. When PE is used in combination with PS, for example, this combination falls into #7 plastics. Containers that contain PE are currently used to package baby food such as Nestlé's Gerber Organic line of baby food, which is packaged in PET and PS layered plastic, with the PET layer being the contact layer.

3.3.3 Polylactic Acid (PLA) Containers

PLA containers are currently available in the marketplace. PLA containers are currently used to package baby food (e.g., Groupe Danone's YoBaby line also uses PLA containers). While PLA containers are classified as #7 plastic, PLA is not recyclable but can be compostable. Refer to Appendix A, End of Life Evaluation, for recyclability considerations.

3.3.4 Polystyrene (PS) Containers

PS containers are currently available in the marketplace and are classified as #6 plastic. However, PS is not used as a contact layer in plastics for baby food. For example, Nestlé's Gerber Organic line of baby food is packaged in PET and PS layered plastic, with the PS layer being the outer layer.

3.3.5 Tritan Copolyester™ (Tritan)

Tritan Copolyester™ is manufactured by Eastman Chemical Co. While this alternative is currently available, it is relatively new to the marketplace, having been introduced in 2008. This product is classified as a #7 plastic. One barrier to entry to the marketplace may relate to the cost of mass production because this product is currently under patent. Further, this product is not a likely replacement for infant BPA-products, as its focus on the residential marketplace is based on replacement of polycarbonate plastics as a reusable plastic. Tritan is not expected to be a cost-effective alternative to disposable containers of infant formula and baby foods. End of life considerations may also impact use and availability in the marketplace. Refer to Appendix A, End of Life Evaluation, for end-of-life considerations, since this product is not currently readily recyclable.

3.3.6 Glass Jars with Polyester Coated Lids

Glass jars with polyester coated lids are currently available in the marketplace. However, more information is needed regarding the polyester coating options with respect to additives, application, and functionality. A potential barrier to mass production of this BPA-free alternative may be its higher manufacturing costs in comparison to PP containers (as an example).

3.3.7 Cans Lined With Resins, Such as Oleoresin

Cans lined with baked-on resins such as oleoresin are currently available. Oleoresin is a mixture of oil and a resin extracted from various plants, such as pine or balsam fir. Oleoresin is currently used as a can liner for low-acid foods (e.g., Eden Foods canned beans). Therefore, one potential barrier to mass production is that this alternative is not suitable for high-acid foods like fruit-based baby foods. Also, increased transparency about the technology of oleoresin linings is needed to fully evaluate the environmental safety of this product.

Oleoresins have an open micellular structure that is susceptible to corrosion (Robertson, 2006). Positives include an ability to withstand the fabrication process as applied to steel cans, but overall, oleoresins have poor adherence and are also not well suited to modern manufacturing processes which require drying times much shorter than the 10-to-15-minute periods typically associated with oleoresins. Finally, oleoresins are widely regarded as having the capacity to impart taste to canned foods (Robertson, 2006, Oldring and Nehring, 2007).

3.3.8 Isosorbide Diglycidyl Ether Coatings

Isosorbide diglycidyl ether coating is undergoing research and development by the New Jersey Institute of Technology (NJIT), among other entities. This coating is derived from corn-based sugars. Both components of the epoxy (the resin and the hardener) are from water-soluble plant-derived chemistries. The primary barrier to entry is that further evaluation of this alternative is necessary with regard to scaled-up production and commercialization costs. Patents have been received by Dr. Michael Jaffe, Biomedical Engineer at NJIT in 2008, and the Iowa Corn Promotion Board (ICPB), but it is unclear if/when this potential BPA alternative will go into high volume production.

3.3.9 Aseptic Cartons (e.g., Tetra Pak)

Aseptic cartons are currently available in the marketplace. A major manufacturer of aseptic packaging is TetraPak. Aseptic cartons are currently used for liquid dairy products (e.g., toddler milk drink boxes) and other liquid products, and it is unknown if/when aseptic packaging may be used for infant formula. A potential barrier to entry to mass production worth noting is that aseptic cartons consist of paper (about 70% of the package), LDPE (24%) and aluminum foil (6%), and the recycling infrastructure must evolve to accommodate access to carton recycling centers. Refer to Appendix A, End of Life Evaluation, for recyclability information for this product. While not currently used for infant formula, aseptic containers are regarded as an option for formula and food packaging. When cost considerations are evaluated, aseptic cartons represent a lower overall cost and energy intensive packaging alternative to aluminum or steel cans for infant formula packaging.

3.3.10 Laminated Pouches (e.g., Cheer Pak)

Laminated pouches are currently available in the marketplace (e.g., Cheer Pak). Cheer Pak laminated pouches include a polyester outer layer, aluminum foil and a PE or PP inner layer, and are currently used to package baby food. For example, Hero Beech Nut and Hain Celestial Earth's Best use Cheer Pak laminated pouches, while Sprout Foods uses a laminated pouch with PP as the food contact layer in baby food packaging. However, a primary barrier to entry for mass production and availability in the marketplace deals with end of life considerations: laminated pouches are not readily recyclable. Refer to Appendix A, End of Life Evaluation, for recyclability information for this product.

3.3.11 Thermoplastic Nylon (TN)

One of the monomers of TN, bis(4-amino-3-methylcyclohexyl)-methane is associated with elevated inhalation toxicity, skin and eye irritation and has the capacity to act as a sensitizer. Based on this information, TN was not considered a suitable candidate as an infant formula and baby food packaging replacement material.

3.3.12 Polyethersulfone (PES)

One of the monomers of PES, 4,4-dichlorophenyl sulfone, is classified by EPA as very persistent in the environment. Another of the monomers, 1.1'-biphenyl-3,4-diol is toxic to aquatic organisms, and a third monomer, bisphenol S, is regarded as an endocrine disruptor. Based on this information, PES was not considered further as a suitable candidate for infant formula and baby food packaging.

3.3.13 Polysulfone

Polysulfone is a thermoplastic thiosulfone polymer. Polysulfone is approved for food contact applications under FDA 21 CFR 177.1655.However, this material is composed of two monomers, one of which is BPA. BPA, as a fundamental component, eliminates polysulfone as a viable candidate in replacement of infant formula and baby food packaging.

3.3.14 Polyphenylsulfone (PPS)

Polyphenylsulfone is a thermoplastic thiosulfone polymer. One of the monomers of PPS, 1,1'-sulfonylbis 4-chlkorobenzene, is listed in the EPA Persistent, Bioaccumulative, and Toxic Profiler as highly persistent in sediment and air, and persistent in water, and soil, as well as having significant fish toxicity, suggesting that it fails the human health and environmental impact screen. Thus, it was not considered further as a viable alternative to packaging infant formula and baby foods.

3.3.15 Valspar Proprietary Coatings

Valspar has also patented BPA- and aromatic glycidyl ether-free coatings and a method to apply them to metal substrates by conventional means such as brushing, roller coating or spraying. According to the patent, the bisphenol-A (BPA), bisphenol-F, bisphenol-A diglycidyl ether (BADGE) and bisphenol-F diglycidyl ether (BFDGE)-free coatings include an undercoat of a polyester (co)polymer, and an undercoat cross-linker; and an overcoat containing a poly(vinyl chloride) (co)polymer dispersed in a substantially non-aqueous carrier liquid, an overcoat cross-linker and a functional (meth)acrylic (co)polymer. Due to a lack of available information, this option was not pursued further in this report as an alternative. It is noted that vinyl chloride is a known/Class A Human Carcinogen.

3.4 Comparison of Functionality of BPA Alternatives

This discussion provides a comparison of the functionality of BPA alternatives and includes a summary of their advantages and disadvantages.

3.4.1 Polypropylene (PP) Containers

3.4.1.1 Chemical Overview

Polypropylene (PP), CAS 9003-07-0, is a by-product of oil refining processes developed in the 1950s as an alternative to polyethylene. PP is a polymer prepared catalytically from propylene, which differs from HDPE by having an isostatic replacement of a hydrogen atom by a methyl group on alternate carbon atoms in the main chain (HSDB 2012). It is easy to produce and assemble, making it an economically viable material (Lenntech 2012). PP has proved versatile in the marketplace. This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.1.2 Product Markets and Function

Typical PP markets include: food packaging, plastic parts, reusable containers, laboratory equipment, loudspeakers, and automotive components (Keller 2012). PP has FDA approval under FDA Part 177.

3.4.1.3 Human Health and Toxicology Evaluation

According to the polypropylene MSDS, polypropylene does not possess any known toxicological properties.

No acute toxicity considerations with respect to polypropylene were found in the following databases:

- WHO Acute Hazard
- TRI Acute Hazard

- Material Safety Data Sheets
- U.S. NTP Acute Toxicity Studies

Polypropylene is not determined to be carcinogenic, based on a search of the following databases:

- IARC Carcinogens
- U.S. NTP Carcinogens
- California Prop 65 Known Carcinogens
- U.S. EPA Carcinogens
- TRI Carcinogen

Polypropylene is not considered to be an endocrine disruptor based on a search of the following databases:

- Illinois EPA List (taken from: *Report on Endocrine Disrupting Chemicals*, Illinois EPA (February, 1997))
- Keith List (taken from: Lawrence H. Keith's *Environmental Endocrine Disruptors: A Handbook of Property Data*, Wiley Interscience (New York, 1997)).
- Colborn List (taken from: T. Colborn, F.S. Vom Saal and A.M. Soto, "Developmental effects of endocrine-disrupting chemicals in wildlife and humans, "*Environmental Health Perspectives*, 1993, v. 101, pp. 378-384. The current list may be found in: *Widespread pollutants with reproductive and endocrine-disrupting effects*. http://www.ourstolenfuture.org/aboutOSF.htm.
- Benbrook List (taken from: Charles M. Benbrook's, *Growing Doubt: A Primer on Pesticides Identified as Endocrine Disruptors and/or Reproductive Toxicants*, National Campaign for Pesticide Policy Reform (Washington, D.C., September 1996).
- Danish EPA List (taken from Auxiliary Matters with Estrogenic Effects, Danish EPA, April, 2000.
- EU List (taken from: *Towards the Establishment of a Priority List of Substances for Further Evaluation of Their Role in Endocrine Disruption*, Appendix 1, BKH Consulting Engineers and TNO Nutrition and Food Research (June 21, 2000)).

Polypropylene is not assumed to have reproductive or developmental toxicity, based on a search of the following databases:

- CA Prop 65 Developmental Toxin
- U.S. TRI Developmental Toxin
- CA Prop 65 Female Reproductive Toxin
- CA Prop 65 Male Reproductive Toxin
- U.S. TRI Reproductive Toxin

Polypropylene is not listed as a constituent under the following databases:

- UNEP Persistent Organic Pollutant (POP)
- UNEP Prior Informed Consent Chemical (PIC)
- WHO Obsolete Pesticide
- U.S. EPA Registered Pesticide
- U.S. EPA Hazardous Air Pollutant
- U.S. EPA Minimum Risk Pesticide (25b list)
- California Registered Pesticide
- California Groundwater Contaminant
- California Toxic Air Contaminant

3.4.1.4 Environmental Evaluation

Ecological toxicity is expected to be very low based on insolubility in water and no known toxicological properties.

According to the Clean Production Action (CPA) Plastics Scorecard (v. 1.0), PP has a maximum attainable grade of A-, indicating general excellence in the marketplace with respect to post-consumer recycled content, primary and intermediate chemicals, catalyst and additives and an assessment of chemical releases and breakdown products. The major variables affecting PP grade are the use of safer additives and catalysts, and higher levels of post-consumer recycled PP content in products.

3.4.1.5 US Patent Information

Patents exist for different formulations of plastics that contain PP and other plastics. However, PP containers are readily made by various manufacturers.

3.4.1.6 Advantages and Disadvantages

3.4.1.6.1 Production Cost

An advantage of PP containers is that they are economical and relatively inexpensive to manufacture in comparison to other alternatives (aseptic cartons, e.g.,).

3.4.1.6.2 Rigidity/Flexibility of Plastic

PP containers are more rigid than PE plastics and have a higher temperature limit to maintain form and function than PE.

3.4.1.6.3 Durability

PP has proved versatile in the marketplace due to its impact strength, resistance to repetitive stress, chemical resistance, and ease of

use/processability (Keller 2012). However, a durability disadvantage with PP containers occurs when containers are subjected to low temperatures for prolonged periods, lowering impact strength.

An advantage of PP containers is that they have a high melting point.

3.4.1.6.4 Weight Characteristics

An advantage is that PP plastic is a stiff, lightweight plastic.

3.4.1.6.5 Shelf Life

PP containers are regarded as having a long shelf-life, including effective protection against exposure to light and heat, transmission of gases (including humidity), mechanical stresses, and contamination by things such as micro-organisms.

3.4.1.6.6 Reactivity

An advantage of PP containers is that they are considered microwave and dishwasher safe. According to a study on the effects of microwave radiation on PP food containers, the plastic containers are considered safe, passing all FDA and EPA tests (Torrison 1999). PP containers have heat aging resistance, meaning that they are usable for hot food products and liquids and can be used repeatedly.

A disadvantage of PP containers is that they degrade in UV light. However, additives may be included in some formulas to stabilize UV light reaction (Lenntech 2012).

A disadvantage of PP containers, as with all resins/plastics, is that PP containers are not biodegradable.

A disadvantage of PP containers is that they are flammable. However, retardant grades are available. PP containers present as sometimes "cloudy," without the glass-like clarity of some polycarbonates. Other disadvantages include factors such as PP containers are difficult to bond, they are degraded by chlorinated solvents and aromatics, and several metals accelerate oxidative degrading.

3.4.1.6.7 Product Sealing and Reuse

PP containers containing liquids typically have a twist cap that allows the container to be repeatedly opened and closed, but closing the container again after it has been opened does not constitute an air-tight "re-sealing" of the container.

PP containers can be reused.

3.4.1.6.8 End of Life Considerations

PP is not accepted at all recycling centers. Recycling centers for #5 plastic (PP) are relatively widespread in the State of Maine. Please refer to Appendix A for end of life considerations.

3.4.1.7 Benchmark Scores

The Plastic Scorecard overall ranking is A- to F. However, CPA notes that with the use of "safer" additives and catalysts, and higher levels of post-consumer recycled PP content, PP could attain Grade A-. It is also worth noting that Propylene (used in making PP plastic) is a Green Screen "yellow" chemical and scored PP as an A+ in two manufacturing categories. The wide fluctuation in score is due to the varying additives and catalysts that can be used in PP production and the post-consumer recycled content (CPA 2012).

3.4.1.8 State of Maine List Status

PP is not listed on the State of Maine Chemicals of Concern List.

3.4.2 Polyethylene (PE) Containers

3.4.2.1 Chemical Overview

Polyethylene (PE), CAS 9002-88-4, is made from natural gas; ethylene, propylene, and other monomers are extracted from the gas (BPI 2012). PE is the largest volume commercial polymer, with billions of pounds produced each year. There are hundreds of variations of PE, including low density polyethylene (LDPE), high density polyethylene (HDPE) and polyethylene terephthalate (PET) (BPI 2012). Production of a polyester resin is achieved by condensing an acid with one or more alcohols or epoxides with copolymerization with cross-linking agents (Robertson, 2006). This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.2.2 Product Markets and Function

There are hundreds of variations of PE resins for a range of uses; PE resins are used to produce gallon milk jugs, motor oil containers, bags, shrink film, automotive parts, various bottles, toys, artificial knee and hip replacement parts, and pallets (UL IDES 2012a; BPI 2012).

Polyester resin coatings are not approved for use with acidic foods, due to hydrolysis of the ester bond, but otherwise, polyesters are varied in their composition and utility. Polyester resins can be made to be extremely flexible or very hard, depending on the resin blending (Oldring and Nehring, 2007). Polyester does not impart any taste or odor to food. In the PET form,

polyethene/polyester resins are used as a laminate currently, covering an underlying BPA layer. This over layer reduces, but does not eliminate, BPA leaching into canned products.

PET is made from the polymerized terephthalic acid and monoethylene glycol. PET is a common material used in disposable bottles and is demonstrated to be cost-competitive in the marketplace for single-use containers.

HDPE is currently used in the manufacture of single use and reusable water bottles. HDPE meets FA approval under FDA Part 177

3.4.2.3 Human Health and Toxicology Evaluation

Regarding PET, FDA has determined that PET is acceptable to use in the applications for which it has been tested (e.g., food applications) (PIO 2012).

PE, HDPE, LDPE and PET are all considered non-hazardous and in widespread commercial use. Non-hazardous classification is consistent with the OSHA Hazard Communication definition. There are no established acute inhalation oral exposure limits and no adverse reproductive or developmental effects. No adverse health effects are anticipated form the reasonable use of this product as a food packaging agent.

Excerpt from *Final Report on the Safety Assessment of Polyethylene*, International Journal of Toxicology, 26(1) 115-127 (2007):

Cellular and tissue responses to polyethylene, determined as part of implant biocompatibility testing, include fibrous connective tissue build-up around the implant material that varies as a function of the physical form of the implant material. Specific assays for osteoblast proliferation and collagen synthesis demonstrated a reduction as a function of exposure to Polyethylene particles that is inversely related to particle size. The effect of Polyurethane particles on monocyte-derived macrophages, however, had a stimulatory effect, prolonging the survival of these cells in culture. The LD_{50} for Polyethylene, with an average molecular weight of 450, in rats was >2000 mg/kg. For Polyethylene with an average molecular weight of 655, the LD_{50} was >5.0 g/kg. Toxicity testing in rats shows no adverse effects at Polyethylene (molecular weight not given) doses of 7.95 g/kg or at 1.25%, 2.50%, or 5.00% in feed for 90 days. Dermal irritation studies on rabbits in which 0.5 g of Polyethylene (average molecular weight of 450) was administered in 0.5 ml of water caused no irritation or corrosive effects; Polyethylene with an average molecular weight of 655 was a mild irritant. Polyethylene (average molecular weight of 450) did not cause dermal sensitization in guinea pigs tested with 50% Polyethylene (*w/w*) in arachis oil BP. Polyethylene, with a molecular weight of 450 and a molecular weight of 655, was a mild irritant when tested as a solid material in the eyes of rabbits. Rabbit eyes treated with a solution containing 13% Polyethylene beads produced minimal irritation and no corneal abrasions. No genotoxicity was found in bacterial assays.

No chemical carcinogenicity has been seen in implantation studies, although particles from Polyethylene implants can induce so-called solid-state carcinogenicity, which is a physical reaction to an implanted material. Occupational case reports of ocular irritation and systemic sclerosis in workers exposed to Polyethylene have been difficult to interpret because such workers are also exposed to other irritants. Clinical testing of intrauterine devices made of Polyethylene failed to conclusively identify statistically significant adverse effects, although squamous metaplasia was observed. The Cosmetic Ingredient Review (CIR) Expert Panel did not expect significant dermal absorption and systemic exposure to large Polyethylene polymers used in cosmetics. The Panel was concerned that information on impurities, including residual catalyst and reactants from the polymerization process, was not available. The Panel considered that the monomer unit in Polyethylene polymerization is ethylene. In the United States, ethylene is 99.9% pure. The other 0.1% includes ethane, propylene, carbon dioxide, carbon monoxide, sulfur, hydrogen, acetylene, water, and oxygen. The Panel believed that the concentration of these impurities in any final polymer would be so low as to not raise toxicity issues. Safety tests of cosmetic-grade Polyethylene have consistently failed to identify any toxicity associated with residual catalyst. The absence of any chemical carcinogenicity in implant studies suggests no genotoxic mechanism for carcinogenicity.

3.4.2.4 Environmental Evaluation

There are no known or established environmental or ecological ramifications based on the use of PE, HDPE, LDPE or PET as a food packaging material. These materials are not considered to have established ecotoxicological considerations and do not bioaccumulate.

3.4.2.5 US Patent Information

Although US Patents exist for various uses and manufacturing additives for use in the development of polyethylene products, polyethylene is not a proprietary chemical.

3.4.2.6 Advantages and Disadvantages

3.4.2.6.1 Production Cost

An advantage of PE containers is low production cost and ease of processing to form a variety of containers, including food containers.

3.4.2.6.2 Rigidity/Flexibility of Plastic

An advantage of PE containers is that they are available in a variety of flexibilities, depending on the production process.

3.4.2.6.3 Durability

PE plastics score fair overall on durability. For example, PET, a variation of PE, has become the plastic packaging of choice for many food products due to its lightweight, large-capacity and shatter-resistant containers.

However, a potential disadvantage is that LDPE and HDPE generally have lower stiffness in comparison to PP containers, and are subject to scratches.

3.4.2.6.4 Weight Characteristics

As with other BPA alternatives like PP containers, PE containers are lightweight and desirable to consumers.

3.4.2.6.5 Shelf Life

PE is a good selection for thermoplastics requiring moisture resistance and low costs (UL IDES 2012a). PE has excellent food preservation capacity and PE containers of even very reactive materials such as hydroxides, acids, and alcohols frequently have shelf lives in excess of one to two years.

3.4.2.6.6 Reactivity

PE is not reactive, based on the MHIS and NFPA agency classifications. An advantage of PE containers is that they are a good option for thermoplastics requiring moisture resistance and low costs, and PE containers provide resistance to gas and liquid movement across the plastic barrier. (UL IDES 2012a).

An additional advantage is that most PE containers are microwavable, but product labeling should be followed.

However, there are disadvantages to the use of PE containers. PE containers are flammable with no preferred flame resistant PE options available.

Another disadvantage is that not all PE containers are dishwasher safe. Again, product labeling should be followed.

PE is not biodegradable.

3.4.2.6.7 Product Sealing and Reuse

PE containers containing liquids typically have a twist cap that allows the container to be repeatedly opened and closed, but closing the container

again after it has been opened does not constitute an air-tight "re-sealing" of the container. The shelf-life of a product is dependent on how the product is stored and handled.

PE containers can be reused.

3.4.2.6.8 End of Life Considerations

An advantage of PE containers is that they are readily recyclable. Please refer to Appendix A for end-of-life considerations.

3.4.2.7 Benchmark Scores

A Plastics Scorecard ranking of C- to F was assigned to PET by Clean Production Action (CPA). Antimony trioxide, a suspected carcinogen, is used as a catalyst in PET production, lowering the overall manufacturing score and directly impacting the Use and End-of-Life score, as antimony trioxide could be released during recycling or incineration (CPA 2012).

3.4.2.8 State of Maine List Status

PE is not listed on the State of Maine Chemicals of Concern List.

3.4.3 Polylactic Acid (PLA) Containers

3.4.3.1 Chemical Overview

Polylactic Acid (PLA), CAS 33135-50-1, is a plastic substitute made from plant starch (e.g., corn and other crops) and is quickly becoming a popular alternative to petroleum-based plastics (West 2012). PLA is produced from corn, a renewable resource. Corn is harvested and then milled to extract starch from the raw materials. Dextrose is produced from the starch and is then fermented, transforming into lactic acid. The lactic acid is altered into a polymer by a chemical process called condensation, thus forming long chain molecular compounds into 4 polylactic acid (Balkcom et al. 2010).

The production of PLA uses 65% less energy than producing conventional plastics. In addition, PLA production generates 68% fewer greenhouse gases (GHG), and contains no known toxins (Cereplast 2011). This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.3.2 Product Markets and Function

Common uses include food containers, bags, bottles, cups, film, and lids (UL IDES 2012b).

3.4.3.3 Human Health and Toxicology Evaluation

As a corn starch-based product, there are no health considerations associated with PLA. Based on efforts to improve durability, additives, such as plasticizers have been considered for use with PLA products. Plasticizers are an added substance to the molecular chain and therefore can be leached from the emulsion. Heat is the preeminent consideration in plasticizers leaching from polymers: the more a polymer with a plasticizer additive is exposed to heat, the greater the potential for the plasticizer to leach from the polymer into the food/containerized material. This is a cause for concern for the product and more importantly the people using the product. This is of greater concern when there is direct contact with containerized food into which plasticizers can leach. The health effects of plasticizers have been scrutinized; however, the risks still remain unclear. In some formulations, up to 5% of the plasticizer's weight can be lost at temperatures of 125 degrees Celsius, and up to 14% of its weight at temperatures of 150 degrees Celsius (Ning, 2010).

3.4.3.4 Environmental Evaluation

There are no significant adverse environmental or ecotoxicological considerations associated with PLA as a corn starch-based product.

3.4.3.5 US Patent Information

Various US patents have been awarded to entities for use and production of PLA. Generic PLA is not a proprietary composition.

A bio-based, sustainable bioplastics manufacturer, Cereplast, has received patent number 8,222,320 for high heat resistant poly compositions containing PLA from the US Patent and Trademark Office.

3.4.3.6 Advantages and Disadvantages

Some of the problems with PLA are with its production. A massive amount of corn is needed to produce PLA. In 2010, 116,000 metric tons of PLA were expected to be in use by 2011 (Kingsland, 2010). The demand for corn can be calculated using the conversion of 2.5 kg of corn needed to produce 1 kg of PLA.

Calculation of corn required for 116,000 metric tons of PLA
116,000 t (of PLA projected) x 2.5 (kg of corn need per 1 kg of PLA) = 290,000.00 t

Therefore, you would need 290,000 metric tons of corn to meet these PLA demands. The USDA projected 2013 corn crop is 273.8 million metric tons. The demand for corn has many competing markets, including ethanol fuel (40% of market), animal feed (40% of market) and food production (20% of market). It is

unclear how these competing demands will affect PLA production, availability and cost.

3.4.3.6.1 Production Cost

PLA is inexpensive, costing less than $1.10 per pound to produce (Cereplast 2011).

3.4.3.6.2 Rigidity/Flexibility of Plastic

PLA containers are relatively flexible. PLA can be modified to run in conventional forming systems such as; injection molding, blow molding, thermoforming, and sheet extrusion (Balkcom et al. 2010). After forming, PLA can hold its shape and be used as a package under normal conditions.

PLA by nature is a brittle polymer; which greatly reduces the usability of the resin. One of the best qualities of polymers is their flexibility that makes them very durable. A possible solution to make PLA a flexible polymer is the addition of plasticizers. The addition of plasticizers may have health considerations not typically associated with PLA and not well studied at this time.

3.4.3.6.3 Durability

PLA is impact-resistant, and can be modified to run in conventional forming systems such as injection molding, blow molding, thermoforming, and sheet extrusion (Balkcom et al. 2010).

3.4.3.6.4 Weight Characteristics

PLA containers and other PLA applications are considered lightweight materials among the materials considered in this assessment.

3.4.3.6.5 Shelf Life

Compared to PET, uncolored PLA bottles have approximately eight times the transmission rate for both water and oxygen. However, adding colorants to the resin can reduce the transmission rates. If the product (e.g., liquid formula) is water-based, PLA might not be the best choice for extended shelf life (more than several months). For moisture-sensitive products, the industry recommends testing to determine compatibility.

PLA is compostable and biodegradable in industrial composting conditions, but it will not degrade or disintegrate on shelves. In order to degrade, PLA must be exposed to temperatures greater than 140°F and relative humidity greater than 90% for approximately 60 to 80 days.

3.4.3.6.6 Reactivity

After forming, PLA can hold its shape and be used as a package under normal conditions. However, once exposed to the proper combination of oxygen, moisture and naturally occurring organisms, it will break down into carbon dioxide, water and a small amount of nontoxic waste (Reeves, 2011). Some studies have shown that it can take as long as 15 months for PLA to start to decompose, even in a controlled composting environment (Rudeekit et al. 2010).

PLA containers have a low melting point. NatureWorks LLC recommends PLA products be stored at a temperature of 105°F or less (NatureWorks 2012). This could potentially create transportation and storage issues (i.e., higher costs for refrigeration or cooling of non-perishable products) in warmer months in several regions of the U.S. However, PLA container characteristics are conducive for cold-storage products.

PLA containers are not microwave or dishwasher safe due to its low melting point.

PLA containers are biodegradable and compostable.

3.4.3.6.7 Product Sealing and Reuse

PLA containers are re-sealable (i.e., lids are used to close the package). Once opened, product reuse ties are typically driven by efficiency of sealing, treatment and storage conditions.

3.4.3.6.8 End of Life Considerations

PLA is considered compostable, but there are limitations. Companies like Coca-Cola have considered bottling their PET-based products with 25% PLA content. There are associated disadvantages in that the PLA content may render a recyclable bottle as non-recyclable and non-biodegradable. Refer to Appendix A for end of life considerations.

3.4.3.7 Benchmark Scores

A Plastics Scorecard ranking of A- to F was assigned to PLA by the Clean Production Action. Although PLA scored an A+ for the usage of a starch and sugar (and the resulting lactic acid), the score was largely affected by the Feedstock Production categories as there are many variables associated with the pesticides used, the crop source (e.g., in the U.S.), and the feedstock source. Additional fluctuations in the score were based on the catalysts and additives used in production (CPA 2012).

3.4.3.8 State of Maine List Status

PLA is not listed on the State of Maine Chemicals of Concern List.

3.4.4 Polystyrene (PS) Containers

3.4.4.1 Chemical Overview

Polystyrene (PS), CAS 9003-53-6, is a polymer made from the monomer styrene, CAS 100-42-5. Properties of PS make it easily injected and molded (UL IDES 2012c), making it a versatile plastic. The primary concern in the use of PS containers is the potential for styrene to leach into foods. Many foods packaged in PS contain levels of styrene (ATSDR 2010). Additionally, there is a negative public perception regarding PS because carcinogenic compounds like styrene and benzene are used in production and there are also contributions to greenhouse gas effects.

3.4.4.2 Product Markets and Function

PS products include both food service packaging (cups, plates, bowls, trays, clamshells, meat trays, egg cartons, yogurt and cottage cheese containers, and cutlery) and protective packaging (shaped end pieces used to ship electronic goods and loose fill "peanuts" (Stromelt 2012)).

3.4.4.3 Human Health and Toxicology Evaluation

PS (plastic #6) was identified by the Pediatric Environmental Health Specialty Units (PEHSU) as a “plastic to avoid” because styrene is a “potentially toxic chemical” (PEHSU 2008).

The Department of Health and Human Services (DHHS), National Toxicology Program (NTP) listed styrene as "reasonably anticipated to be a human carcinogen" in the Report on Carcinogens, Twelfth Edition, released on June 10, 2011. Also, the International Agency for Research on Cancer (IARC) has determined that styrene is a possible carcinogen.

While adverse effects, including cancer, may result from exposure to styrene, it is important to note that inhalation exposure is the primary route of exposure. Ingestion of styrene in foods packaged in PS containers has not been shown to cause cancer. According to ATSDR, there are no reports of cancer resulting from styrene exposure by the oral or dermal routes in humans (ATSDR 2012).

The following is excerpted from the ATSDR Toxicological profile for styrene (ATSDR 2010):

Styrene-induced neurotoxicity has been reported in workers since the 1970s. Studies over the last 15 years have firmly established the central nervous system as the critical target of toxicity. Both short- and long-term exposures to styrene can result in neurological effects. Acute exposure data are limited to the finding of impaired performance on tests of vestibular function in test subjects exposed to 87– 376 ppm for 1–3 hours and studies finding no alterations in performance of neurobehavioral tests (reaction time, color discrimination, and tests of memory or attention) in subjects exposed to 20 or 49 ppm (ATSDR 2010). A variety of neurological effects have been observed in chronically exposed styrene workers; these effects include decreased color discrimination, vestibular effects, hearing impairment, symptoms of neurotoxicity, particularly "feeling drunk" and tiredness, delays in reaction time, impaired performance on tests measuring attention and memory, increased vibration perception thresholds, impaired nerve conduction velocity, and EEG alterations (ATSDR 2010). The LOAELs for these effects range from about 10 ppm to 93 ppm (ATSDR 2010). In most of the occupational exposure studies, neurological function tests were conducted in the morning before work, suggesting that the deficits were not acute effects. Results of a meta-analysis suggest that the severity of the some of the neurological symptoms increases with exposure duration. For example, 8, 15, 25, and 35% increases in reaction time were observed in workers exposed to 100 ppm for 2, 4, 6, and 8 work-years, respectively (ATSDR 2010). However, this may also be reflective of higher exposure levels in the past rather than a duration-related increase in severity. The existing data are inadequate to determine whether chronic styrene exposure results in permanent damage. Mixed results have been found in studies examining workers before and after an extended period without styrene exposure. Neurotoxicity studies in animals have primarily focused on effects on hearing and damage to the organ of Corti.

Other effects that have been observed in animal studies include damage to the nasal olfactory epithelium and liver necrosis; testicular damage and developmental effects have also been reported, but the weight of evidence does not support concluding that these are sensitive targets (ATSDR 2010). Damage to the nasal olfactory epithelium was observed in mice after 3 days of exposure (ATSDR 2010). The severity of the lesion progressed from single cell necrosis to atrophy and respiratory metaplasia with increasing exposure duration. The lowest-observed-adverse-effect levels (LOAELs) for these lesions are 80, 50, and 20 ppm for acute, intermediate, and chronic exposure, respectively (ATSDR 2010). Rats do not appear to be as sensitive as mice to the nasal olfactory epithelial damage; an intermediate-duration study identified a no-observed-adverse-effect level (NOAEL) and LOAEL of 500 and 1,000 ppm for focal hyperplasia and a chronic study identified a LOAEL of 50 ppm for atrophy and degeneration (ATSDR 2010). The observed species differences may be due to differences in styrene metabolism in the nasal cavity. In particular, rats have a higher capacity to detoxify styrene oxide with epoxide hydrolases and glutathione S-transferase (ATSDR 2010). Humans are not likely sensitive to the nasal toxicity of styrene

because styrene oxide has not been detected and high levels of epoxide hydrolases have been found in *in vitro* assays of human nasal tissue.

Unlike the nasal lesions, the severity of hepatic lesions decreases with increased exposure durations. Severe hepatocellular necrosis was observed in mice exposed to 250 ppm for 3 days; however, continued exposure at this concentration resulted in focal necrosis and an increase in pigmented macrophages (ATSDR 2010). Centrilobular aggregates of siderophages were observed in mice exposed to 200 ppm for 13 weeks; no liver effects were observed at 160 ppm after 2 years of exposure (ATSDR 2010). Rats are less sensitive than mice to liver toxicity; no liver effects were observed in an intermediate-duration study in which rats were exposed to a styrene concentration 10-fold higher than the concentration eliciting hepatic effects in mice (ATSDR 2010). No alterations in serum markers of liver damage were observed in styrene workers exposed to 40 ppm for approximately 5 years. Liver effects have not been observed in rats orally exposed to 35 mg/kg/day for 105 weeks. Some hepatic alterations (increases in liver weight and small areas of focal necrosis) have been reported in rats exposed to 400 mg/kg for an intermediate duration; however, the studies are poorly reported and lack statistical comparisons with controls. No studies examined systemic end points following acute exposure.

Occupational exposure studies have not found significant increases in the occurrence of stillbirth, infant death, malformations, or low birth weight. An increase in fetal deaths was observed in hamsters exposed to very high concentrations (1,000 ppm on gestation days 6–18) and in rats exposed to 300 ppm on gestation days 6–20. However, most single and multi-generation inhalation and oral exposure animal studies did not find significant alterations in fetus/pup survival, growth, or incidence of abnormalities in rats, mice, rabbits, and hamsters exposed to styrene (ATSDR, 20210). Two studies have examined neurodevelopmental effects in rats; one study found some minor effects (slight delays in some developmental landmarks). The other, higher-quality study did not find any significant alterations in a number of neurodevelopmental end points. The National Toxicology Program (NTP) Expert Panel examining the developmental potential of styrene concluded that the human data are not sufficient to evaluate the potential developmental toxicity of styrene in humans and that there was no convincing evidence of developmental toxicity in animals (ATSDR 2010).

Although several epidemiology studies have examined potential reproductive effects in male and female styrene workers, adequate analysis of the data is limited by the lack of exposure information and concomitant exposure to other compounds. Mixed results have been found for increased occurrence of spontaneous abortions and oligomenorrhea (ATSDR 2010). In male workers, sperm abnormalities have been reported (Kolstad et al. 1999a), but not alterations in time-to-pregnancy or fertility rates. No adverse reproductive effects were observed in inhalation and oral multi-generation studies in rats. A series of studies

found decreases in spermatozoa counts in rats exposed as adults, as neonates, and through lactation. However, as noted by the NTP Expert Panel, this finding is not consistent with the lack of reproductive effects found in the inhalation two-generation study (ATSDR 2010). The NOAEL identified in the two-generation inhalation study was 500 ppm (6 hours/day), which is roughly equivalent to 230 mg/day using a reference inhalation rate of 0.42 m^3/day (ATSDR 2010). The LOAEL for spermatozoa effects in adult rats was 400 mg/kg (6 days/week), which is roughly equivalent to 158 mg/day using a reference body weight of 0.462 kg (ATSDR 2010).

There are several epidemiologic studies of workers at styrene manufacturing and polymerization facilities and reinforced plastics facilities that suggest an association between occupational exposure and an increased incidence of cancer of the lymphatic and hematopoietic tissues in styrene. However, the reported studies are inconclusive due to exposure to multiple chemicals (including benzene) and the small size of the cohorts. Other studies have reported negative results. More consistent results for increases in the risk of lymphatic and hematopoietic cancers have been observed among workers at styrene-butadiene manufacturing facilities (ATSDR 2010). There is suggestive evidence that these increased risks may be due to exposure to 1,3-butadiene rather styrene exposure; however, it is difficult to separate the risks for styrene and 1,3-butadiene because the exposure is highly correlated (ATSDR 2010).

There are no reports of cancer resulting from styrene exposure by the oral or dermal routes in humans. Species differences in styrene carcinogenicity have been detected in animal studies.

Inhalation and oral exposure studies in rats have not found significant increases in neoplastic lesions. However, increases in lung tumors have been found in mice following inhalation and oral exposure. The increased production of styrene 7,8-oxide in lung Clara cells and the higher ratio of styrene oxide R-to S-enantiomers likely resulted in the increased sensitivity of mice.

Overall, human and animal studies suggest that styrene may be a weak human carcinogen. The IARC has assigned styrene to Group 2B, possibly carcinogenic to humans (ATSDR 2010). EPA and DHHS have not evaluated the carcinogenic potential of styrene. One study lists a cancer classification of A4, not classifiable as a human carcinogen based on a 1996 evaluation of the available data.

3.4.4.4 Environmental Evaluation

Styrene will be emitted to air from industrial processes that use or manufacture the material or where it is formed as a by-product.

Although other aromatic compounds (e.g., benzene, toluene, polycyclic aromatic hydrocarbons (PAH), etc.) have been thoroughly studied over the years, styrene

has been given little attention probably due to its lower rate of industrial use. In addition, it is less toxic than benzene and PAH, proven carcinogens. However, it is classified as a mutagen and thus potentially carcinogenic (ATSDR 2010). Its main use is in the production of the polymer polystyrene and in the production of plastics, rubber, resins, and insulators (Gibbs 1997). Entry into the environment is mainly through industrial and municipal discharges. The data on short- or long-term exposures to plants, birds, and land animals are insufficient to be conclusive (Gibbs 1997).

Styrene is moderately toxic to aquatic organisms. Styrene is expected to have low toxicity towards terrestrial animals. Styrene contributes to the formation of photochemical smog due to indirect photochemical reactions.

Styrene will be transported as a vapor in air, in water and in contaminated soils. Styrene has a slight tendency to bioaccumulate.

Styrene is quickly broken down in the air, usually within one to two days; it evaporates from shallow soils and surface water. Styrene that remains in soil or water may be broken down by bacteria. Styrene Monomer is non-persistent in water, with a half-life of less than 2 days. About 99% of Styrene Monomer will eventually end up in air; about 0.85% will end up in water; the rest will end up in terrestrial soils and aquatic sediments (NPI 2012).

3.4.4.5 US Patent Information

Many US patents exist for the production and handling of polystyrene, usually associated with specific compositions or additives. Generic polystyrene is not a proprietary chemical or product.

3.4.4.6 Advantages and Disadvantages

3.4.4.6.1 Production Cost

An advantage of PS containers is that they are inexpensive to produce.

3.4.4.6.2 Rigidity/Flexibility of Plastic

PS containers have a high level of rigidity.

3.4.4.6.3 Durability

PS containers are highly impact resistant.

3.4.4.6.4 Weight Characteristics

PS containers are lightweight.

3.4.4.6.5 Shelf-Life

Polystyrene disposable food packaging has the same or similar qualities of other plastics, including protection against bacteria and moisture with a generally long shelf life.

3.4.4.6.6 Reactivity

The primary disadvantage of using PS containers is that styrene may be released from containers made of PS foam when they are heated or used to store foods/liquids at temperatures exceeding 80°F (PEHSU 2008). PS is preferred as an outer layer in layered plastics.

Given the poor thermal stability of PS containers, many PS containers are not microwaveable or dishwasher safe.

PS containers are flammable, though retardant grades are available.

PS containers are not biodegradable.

3.4.4.6.7 Product Sealing and Reuse

PS containers can be designed with lids or caps for reuse.

3.4.4.6.8 End of Life Considerations

PS containers are recyclable. Refer to Appendix A for end of life considerations.

3.4.4.7 Benchmark Scores

Information on a GreenScreen score for PS containers is not currently available. A GreenScreen for PS was not advanced as a component of this report as PS was not identified as a preferred alternative to BPA-based packaging for infant formula and foods.

3.4.4.8 State of Maine List Status

Styrene is listed on the State of Maine Chemicals of High Concern List as an endocrine disruptor.

3.4.5 Tritan Copolyester™ (Tritan)

3.4.5.1 Chemical Overview

Eastman Tritan™ copolyester, a novel plastic from Eastman Co., is manufactured utilizing three monomers: di-methylterephthalate (DMT), 1,4-

cyclohexanedimethanol (CHDM), and 2,2,4,4-tetramethyl-1,3-cyclobutanediol (TMCD) in various ratios (Osimitz, 2012). As with most polymers, the monomers (along with the high molecular weight oligomers, whose toxicity is most commonly represented by the monomers), make up the predominant amount of free chemicals available for leaching into the environment and/or foods. This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.5.2 Product Markets and Function

Tritan was launched by Eastman Chemicals in October 2008. Tritan is currently in use under a broad range of consumer products, including: reusable bottles, pacifiers, breast pumps, plastic dishware and cutlery, general housewares, small appliances, medical devices, rigid medical packaging, infant care, sports bottles, bulk water bottles, face protection, and outdoor signs. Tritan copolyester has many of the characteristics of polycarbonate, such as toughness and impact resistance. Tritan adds chemical resistance, dishwasher durability and an ability to comply with market-specific standards for sterilization and hygiene (Eastman, 2012a). Tritan can also be manufactured to provide a lightweight, shatterproof alternative to glass with glass-like clarity (Eastman, 2012a). As a proprietary polymer, Eastman offers technical services expertise to partners interested in utilizing Tritan to avoid false start-ups and otherwise limit manufacturing disruptions, including tooling, processing, testing and secondary operations.

3.4.5.3 Toxicology and Human Health Evaluation

Tritan is manufactured utilizing three monomers: di-methylterephthalate (DMT), 1,4-cyclohexanedimethanol (CHDM), and 2,2,4,4-tetramethyl-1,3-cyclobutanediol (TMCD) in various ratios (Osimitz, 2012).

Tritan's™ monomers were evaluated using quantitative structure activity relationship (QSAR) for binding to the androgen receptor (AR) and estrogen receptors (ER) (alpha and beta), as well as a battery of in vitro and in vivo techniques to determine their potential androgenicity or estrogenicity. The findings were universally negative (Osimitz, 2012). When these data are coupled with other in vivo data developed to assess systemic toxicity and developmental and reproductive toxicity, the data clearly indicate that these monomers do not pose an androgenic or estrogenic risk to humans. Additional data presented also support such a conclusion for terephthalic acid (TPA). TPA is also a common polyester monomer and is the main mammalian metabolite formed from DMT (Osimitz, 2012).

- **Quantitative structure activity relationships (QSAR).**[12] Computer modeling of monomers to assess each substance's molecular structure and its ability to bind to

[2] *Conducted by Dr. William Welsh, Department of Pharmacology, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway*
[2] *Conducted by CeeTox Inc, Kalamazoo, Mich.*

human estrogen and androgen (testosterone) receptors in a manner that could lead to their activation.

- **Receptor transactivation assays.**[2, 3] The estrogenic and androgenic activity of both the monomers and concentrated extracts of Tritan also were evaluated in vitro using both yeast and mammalian cell assays performed by two separate labs. These tests evaluate a substance's ability to bind to a hormone receptor and, induce gene expression. Extracts were generated using U.S. Food and Drug administration (FDA) and European (specifically, Commission Regulation (EU) No. 10/2011) recommendations for food contact migration testing. Additional extracts were derived following a dishwasher simulation environment (10 days, 70ºC in Cascade® solution).

- **Competitive binding assays.**[2] Despite the fact that neither the QSAR nor transactivation studies showed any evidence of binding or gene expression by estrogenic or androgenic pathways, a second tier of tests based on competitive binding assays was conducted. These tests can confirm a substance's ability to specifically bind to a specific hormone receptor and can be used to calculate the relative binding affinity.

- **Uterotrophic assay.** This is considered a definitive test for assessing a chemical's potential to elicit estrogenic or androgenic responses in living biological systems. This in vivo test is part of the Tier I Endocrine Disruption Screening Program of the U.S. Environmental Protection Agency.

- **Hershberger assay.**[4] This is considered a definitive test for assessing a chemical's potential to elicit estrogenic or androgenic responses in living biological systems. This in vivo test is part of USEPA's Tier I Endocrine Disruption Screening Program.

- The uniformly negative responses seen in these complementary third-party studies overwhelmingly demonstrate that Eastman Tritan™ copolyester is free of estrogenic and androgenic activity.

  The in vivo uterotrophic and Hershberger assays utilized in Osimitz, 2012, are considered the definitive tests for assessing a chemical's potential to elicit estrogenic activity (EA) or androgenic activity (AA) responses and they are part of the Tier 1 Endocrine Disruption Screening Program.

  In 2009, Eastman contracted with an independent third-party laboratory to test cytotoxicity, sensitization reactions and skin irritation response associated with Tritan. All test results were reported as negative (Eastman, 2012b).

- Cytotoxicity: An agar diffusion test was conducted to evaluate the potential biological reactivity of mammalian cells in vitro. Mammalian cells were selected

[3] *Conducted by the Center for Environmental Biotechnology, University of Tennessee, Knoxville*
[4] *Conducted by WIL Research Laboratories, LLC, Ashland, Ohio*

for the test because of their sensitivity to leachable cytotoxic substances. There was no biological reactivity observed after 48 hours post-exposure. These results tend to indicate that Tritan is non-cytotoxic (Eastman 2012b).

- Sensitization Reactions: A direct contact Buehler sensitization test was conducted to evaluate potential to produce skin sensitization in mammalian tissues in vivo. Topical application was selected because it represents a likely route of human exposure for infant care products. No skin reactions or overt signs of toxicity were detected (Eastman 2012b).
- Skin Irritation Responses: A primary skin irritation test was conducted to evaluate the potential to produce primary dermal irritation after a single topical exposure. Dermal exposure was selected because it represents a likely route of human exposure for infant care products. There were no signs of erythema (redness) or edema (swelling) at any point during the observation period (Eastman 2012b).

All studies were conducted in accordance with the current FDA 21 CFR, Part 58 – Good Laboratory Practice for Non-Clinical Laboratory Studies (Eastman, 2012b).

Tritan is GREENGUARD Indoor Air Quality Certified (Eastman, 2012b). The GREENGUARD Environmental Institute is an industry independent, not-for-profit organization that provides and implements the voluntary third-party GREENGUARD Certification Program. The program currently includes two product certification types, GREENGUARD Indoor Air Quality Certification and GREENGUARD Children & Schools Certification.

Both certifications qualify low-emitting products through rigorous testing and suppliers. All GREENGUARD Certified products carry a GREENGUARD Certification mark, and are listed in the free online GREENGUARD Product Guide. More information available at: http://www.greenguard.org/en/indoorAirQuality/iaq_healthImpacts.aspx

Tritan has been cleared for food-contact applications by the U.S. FDA, Heath Canada, the European Food and Safety Authority and China's Ministry of Health (Eastman 2012c)

3.4.5.4 Environmental Evaluation

Tritan is BPA-free and made without halogens, sulfur, nitrogen, lead, mercury, cadmium or hexavalent chromium, helping to keep these contaminants out of the waste stream and greater environment. Aside from the expected health benefit of BPA elimination, Tritan manufacture has significant sustainability implications for the industry.

According to Eastman marketing materials, for every 1 million pounds (453,592 kilograms) of Tritan used in place of traditional polycarbonate, the energy saved is equivalent to 140,000 gallons (530,000 liters) of gasoline. In addition, the decrease in greenhouse gas emissions from using 1 million pounds of Tritan over

traditional polycarbonate is equivalent to taking 390 cars off the road for a year (Eastman, 2012b).

Tritan has a favorable Life Cycle Assessment (LCA) when compared with traditional polycarbonate, including a 13% improvement in energy savings and a 42% lower greenhouse gas (GHG) emission rate (Eastman, 2012b).

3.4.5.5 US Patent Information

The following record is from the CAplus[SM] database: January 1, 2010

CAPLUS COPYRIGHT 2010 ACS

PATENT NUMBER:	EP 1899399
TITLE:	Infant pacifier made of impact-resistant thermoplastic polyester composition
INVENTOR(S):	Crawford, Emmett Dudley; Porter, David Scott; Connell, Gary Wayne
PATENT ASSIGNEE(S):	Eastman Chemical Company, USA
SOURCE:	U. S., 37pp. CODEN: USXXAM
LANGUAGE:	English

ABSTRACT:

The invention relates to an infant pacifier made of a polyester compound, comprising units of terephthalic acid, 2,2,4,4-tetramethyl-1,3-cyclobutanediol, and 1,4-cyclohexanedimethanol, the polyester having a certain combination of inherent viscosity and glass transition temp. The polyester compound has improved combination of at least two of high impact strength, moderate glass transition temp. Toughness (Tg), inherent viscosity, low ductile-to-brittle transition temperatures, good color and clarity, low density, chemical resistance, and long crystaline halftime, which make it easier to process into articles.

Eur. Patent 1899399, Nov. 18, 2009

3.4.5.6 Advantages and Disadvantages to Use

Eastman production materials tout Tritan as a unique balance of attributes consisting of toughness, heat resistance, ease in processing, chemical resistance, and glass-like clarity to provide functional and aesthetic advantages over other clear thermoplastics, such as polycarbonate, polypropylene styrenic copolymers and acrylics. Tritan copolyester may be a taste-free, odor-free and BPA-free alternative to polycarbonate and other plastics. The principal disadvantage of Tritan appears to be the associated cost, especially compared to polypropylene (see Section 3.4.5.6.1). Tritan appears to be a viable replacement for

polycarbonate; however, Tritan products for the residential market (as targeted by this AAR) are primarily focused on reusable items, such as "sippy" cups and infant bottles. Tritan is under patent, proprietary and not cost-effective for one-time use/disposable packaging for infant formula or foods in the marketplace.

3.4.5.6.1 Production Cost

As a material, Tritan is, reportedly, more expensive than polypropylene. Production cost is lower than those associated with traditional polycarbonate by eliminating energy-intensive processes such as annealing and pre-drying extruded sheet. Tritan requires less energy to process than metal (aluminum) sports bottles.

3.4.5.6.2 Rigidity/Flexibility

Tritan has good processability and may be injection molded or extrusion blow molded and is considered good for use in rigid packaging. It is currently in use as a rigid medical packaging material, which is shatterproof and has glass-like clarity.

3.4.5.6.3 Durability

Tritan is considered to have good durability. It is considered shatterproof and products made from it are considered dishwasher safe due to its chemical and heat resistance. Tritan is currently used to manufacture reusable bulk water containers that can withstand high pressure and temperature washing systems. The durability of Tritan offers opportunities to use less protective packaging compared to glass or brittle polymers.

3.4.5.6.4 Weight Characteristics

Weight translates to additional production and transportation costs. Tritan has a lower density than traditional polycarbonate, which yields more "parts" per pound or kilogram of polymer used. Tritan is significantly lighter weight than glass, reducing shipping energy costs. Tritan has the added benefit of being shatterproof, allowing for downgauging of aspects like wall thickness to reduce material usage and weight.

3.4.5.6.5 Shelf Life

When used as the basis for rigid medical packaging, the durability and heat resistance of Tritan can allow for more rapid accelerated–aging protocol validation and more reliable shelf-life qualification before going to market. Tritan is expected to have comparable shelf-life to other plastics.

3.4.5.6.6 Reactivity

Tritan is consisted chemical resistant and able to comply with market-specific standards for sterilization and hygiene. Tritan is used in the

production of medical devices and can allow the use of common disinfectants and sterilizing techniques, while allowing for greater flexibility with respect to solvent bonding and other secondary operations. It is unknown whether Tritan has particular sensitivity to UV light or whether it is microwaveable; however, it is expected that Tritan will possess many of the same characteristics as traditional polycarbonates. This suggests that Tritan is not susceptible to UV light. Since microwaving most polycarbonates has the potential to liberate BPA, microwaving of polycarbonates is not recommended; however, particular polycarbonates have solved this shortcoming, such as the development of Lexan. Traditional polycarbonate is not biodegradable.

3.4.5.6.7 Product Sealing and Reuse

Depending on the type of closure and manufactured form of a given container, Tritan is expected to have similar resealing capabilities as other plastics.

3.4.5.6.8 End of Life Considerations

As noted above, Tritan has a favorable LCA compared with traditional polycarbonate, including a 13% improvement in energy savings and 42% lower GHG emissions. Reusable sports bottles made from Tritan are considered to have a lower cradle-to-grave environmental impact than metal sports bottles and they require less energy to process and produce. The thermal stability of Tritan permits the complete reuse of all clean, dry regrind in the recycling process.

3.4.5.7 Benchmark Scores

As a copolyester, Tritan is in widespread use and generally considered as inherently safe. In light of available toxicity information, a GreenScreen score was not considered relevant.

3.4.5.8 State of Maine List Status

Neither copolyesters (polyesters) nor the individual monomers composing Tritan are listed on the State of Maine Chemicals of Concern List.

3.4.6 Glass Jars with Polyester Coated Lids

3.4.6.1 Chemical Overview

PET is the chemical name for polyester. When PET is used for fiber or fabric applications, it is usually referred to as "polyester." When used for container and packaging applications, it is typically called "PET" or "PET resin."

Please see Section 3.4.2 and associated subsections for additional information on polyester/polyethylene as primary container materials. This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.6.2 Product Markets and Function

Limited information is available regarding details of using polyester lined lids (or cans). A polyester coating can be used on its own or as an undercoating, which reduces BPA leaching capabilities up to 95% into food and beverages (BCF 2010).

A common polyester resin used for lining metal lids (protecting the steel substrate from corrosion and food contamination) is PET. Please see Section 3.4.2 and associated subsections for additional information on PET as primary container materials. Health and environmental implications are similar when used as a lid coating, although significantly less material enters the market and is available for direct food contact when limited to use as a lid coating.

Additional information is necessary to fully assess the health and safety of polyester coatings. This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.6.3 Human Health and Toxicology Evaluation

Please see Section 3.4.2.3 for a discussion of the human health implications for use of PET in food packaging.

3.4.6.4 Environmental Evaluation

Please see Section 3.4.2.4 for additional discussion of the environmental implications of PET manufacturing and use. Additional information is necessary to fully assess the health and safety of polyester coatings.

3.4.6.5 US Patent Information

Although US Patents exists for various uses and manufacturing additives for use in the development of polyethylene products, polyethylene is not a proprietary chemical.

3.4.6.6 Advantages and Disadvantages

3.4.6.6.1 Production Cost

A disadvantage is that polyester coated metal lids, in combination with the cost of glass jars/containers, are expensive to manufacture in comparison to PP and PE containers.

3.4.6.6.2 Rigidity/Flexibility of Plastic

This section is not applicable for the BPA alternative.

3.4.6.6.3 Durability

A disadvantage of glass jars is that they can be easily broken. Care in shipping and handling of glass containers is needed to prevent breakage.

3.4.6.6.4 Weight Characteristics

Glass jars with metal tops are significantly heavier than plastic.

3.4.6.6.5 Shelf Life

Baby food bottled in glass jars with metal-coated lids has a long shelf-life, provided that the bottling process was completed properly to prevent bacterial contamination.

3.4.6.6.6 Reactivity

An advantage of this BPA alternative is that glass is a nonreactive surface and is suitable as a food contact layer. Refer to Section 3.4.2 regarding PET.

3.4.6.6.7 Product Sealing and Reuse

Glass jars may be resealed and reused.

3.4.6.6.8 End of Life Considerations

While glass can be reused or recycled, a primary disadvantage to this BPA alternative is that the lids are not readily recycled. Refer to Appendix A for end of life considerations.

3.4.6.7 Benchmark Scores

This BPA alternative primarily consists of glass, thus a plastic scorecard score for polyester is not entirely applicable for glass jars of baby food. A Plastics Scorecard ranking of C- to F was assigned to PET by Clean Production Action (CPA). Antimony trioxide, a suspected carcinogen, is used as a catalyst in PET production, lowering the overall Manufacturing score and directly impacting the Use and End-of-Life score, as antimony trioxide could be released during recycling or incineration (CPA 2012).

3.4.6.8 State of Maine List Status

Polyester is not listed on the State of Maine Chemicals of Concern List.

3.4.7 Cans Lined With Baked-on Resins, Such as Oleoresin

3.4.7.1 Chemical Overview

Oleoresin, a mixture of oil and a plant extract resin, is currently available for lining in food cans containing low acidic foods. Oleoresin was used by Ball Corp. prior to the development of epoxy resins, such as BPA. Limited information on Oleoresin technology is available at the time of report production. This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

3.4.7.2 Product Markets and Function

Oleoresin (and other non-epoxy resins) usage among manufacturers appears to be limited; Oleoresin-lined cans costs an average of 20% more than BPA-lined cans (Pierce & Caliendo 2012). As a result of the limited usage in the marketplace, specific data regarding the Oleoresin lining is not widely available.

Oleoresins have an open micellular structure which is susceptible to corrosion (Robertson, 2006). Positives include an ability to withstand the fabrication process as applied to steel cans, but overall, oleoresins havepoor adherence and are also not well suited to modern manufacturing processes which require drying times much shorter than the 10 to 15 minute periods typically associated with oleoresins. Finally, oleoresins are widely regarded as having the capacity to impart taste to canned foods (Robertson, 2006, Oldring and Nehring, 2007).

Eden Foods currently uses an oleoresin coating. Information requests for additional information were not returned.

3.4.7.3 Human Health and Toxicology Evaluation

Oleoresins are composed on three basic types of monomers: zinc oxide, gum rosin, and unsaturated polyester. The oleoresinous ingredient of gum rosin is generally recognized as a safe (GRAS) material. Human health issues related to other ingredients are insignificant. The barriers to introduction do not hinge on human health issues.

3.4.7.4 Environmental Evaluation

Oleoresins are generally recognized as safe (GRAS) materials. The barriers to introduction do not hinge on environmental health issues.

3.4.7.5 US Patent Information

Many patents exist to protect development rights to oleoresins from a number of plant-based sources. The patent review to determine whether any of these are viable candidates for application as a can lining was determined to be beyond the scope of this assessment.

3.4.7.6 Advantages and Disadvantages

3.4.7.6.1 Production Cost

Costs on average run 14 to 20 percent more (varies on size) to produce, compared to BPA-lined cans. This translates to a marginal increase in overall cost transmitted to the consumer of less than $0.03/can.

3.4.7.6.2 Rigidity/Flexibility of Plastic

The BPA alternative is a can lined with a baked-on resin, and therefore this section is not applicable.

3.4.7.6.3 Durability

Cans are considered durable, as they can become dented in shipment but still provide adequate protection of food contents.

3.4.7.6.4 Weight Characteristics

Metal cans have a significantly greater weight associated with them compared to lightweight plastics, such as PE.

3.4.7.6.5 Shelf Life

Canned foods have a long shelf-life provided that the canning process was completed properly to prevent bacterial contamination

and that the can lining will not react or breakdown from food contact.

3.4.7.6.6 Reactivity

A disadvantage of oleoresin is that it cannot be used as can lining for highly acidic foods, such as tomatoes.

3.4.7.6.7 Product Sealing and Reuse

Cans cannot be resealed and are generally not reusable.

3.4.7.6.8 End of Life Considerations

Cans are readily recyclable. Refer to Appendix A for end of life considerations.

3.4.7.7 Benchmark Scores

This section is not applicable for this BPA alternative.

3.4.7.8 State of Maine List Status

Oleoresinous compounds are not listed on the State of Maine Chemicals of Concern List.

3.4.8 Isosorbide Diglycidyl Ether Coatings

3.4.8.1 Chemical Overview

Isosorbide is a sugar (glucose)-derived natural material. It has found use in the form of derivatives in the pharmaceutical industry like isosorbide mononitrate and isosorbide dimethyl ether. Since isosorbide is water soluble and harmless, it can be used as an intermediate for additives and stabilizers in both the cosmetics and plastics industry (Feng, 2010). This BPA alternative does not contain any chemicals of concern identified by the State of Maine.

Depending on the different reactivity of its two hydroxyl groups, isosorbide acts as a nucleus allowing different functionalities to be attached, such as UV-absorbing moieties, antioxidants and plasticizers (Feng, 2010).

Isosorbide can be attached to glycidyl ether or allyl ether to make cross-linkable epoxy resin monomer with similar properties to bis-A diglycidyl ether (Feng, 2010).

Isosorbide is generally known as a monomer for incorporation into polyesters such as polyethylene terephthalate (PET) at low levels (Feng, 2010). Due to the rigid molecular structure of isosorbide, polyester copolymers made by using isosorbide have higher glass transition temperatures (Tg) than PET, with the range from 80℃ to 200℃ (Feng, 2010).

The more the isosorbide monomer is incorporated, the higher the Tg of polyesters with more amorphous phase could be. Because there is growing interest in inexpensive bottle resins, which have a Tg of 86℃, or higher, and can be hot filled and pressurized without distortion, the low cost isosorbide reinforced polyester with attractive thermal stability becomes a very promising candidate for the application of "hot filling" bottles, like tomato ketchup or other condiments that must be pasteurized first. However, incorporation of isosorbide into PET on a commercial scale has encountered several problems. The secondary hydroxyl groups of isosorbide make it less reactive than the primary hydroxyls of ethylene glycol (Feng, 2010). This fact, coupled with the volatility of isosorbide, makes it difficult to get high incorporation into (polyethylene isosorbide terephthalate) PEIT copolymers and leads to complications with the recycle of the ethylene glycol/isosorbide stream generated during polymerization (Feng, 2010). Additionally, the stereochemistry of isosorbide is such that one hydroxide (OH) is endo and one exo: this leads to a pronounced differential reactivity and an overall sluggishness in copolyester formations (Feng, 2010). Usually, only 35 to50 percent of the added isosorbide becomes part of the polymer structure – the rest is lost by evaporation in the high vacuum stage of the polymerization reaction (Feng, 2010).

In order to overcome these shortcomings, isosorbide derived AB monomers were proposed. The chemically modified isosorbide derivatives allow for essentially complete incorporation into high molecular weight polymers like PET and PLLA to raise their Tg (Feng, 2010).

3.4.8.2 Product Markets and Function

Isosorbide's molecular geometry and chemical functionality provide it compatibility with many commercial plastics and specialty additives. The asymmetric reactivity, chirality and controlled stereochemistry in the design and performance of its derivatives, including thermoplastics, thermosets and low molar mass compounds that can act as plasticizers, stabilizers or compatibility-enhancers, make it more commercially attractive in the polymer and specialty chemical industry.

The Iowa Corn Promotion Board (ICPB) of the US agricultural cooperative Iowa Corn Growers Association jointly filed a patent with the

New Jersey Institute of Technology (NJIT) in February, 2010, for a corn-derived epoxy resin that may be able to replace bisphenol A (BPA)-based epoxies as metal can liners.

The epoxy resin granted US patent rights is specifically derived from corn-based isosorbide diglycidyl ether. Both components of the epoxy - the resin and the hardener - are from water-soluble, plant-derived chemistries (Guzman, 2010).

The monoisosorbide diglycidyl ether was prepared by a Williamson ether reaction. Diallyl isosorbide ether was prepared by heating the isosorbide with allyl bromide in sodium hydroxide solution as shown in Scheme1. Freshly-prepared unpurified diallyl isosorbide was treated with the meta-chloroperbenzoic acid in methylene chloride to generate isosorbide diglycidyl ether. Since the isosorbide has two hydroxyl groups with different reactivity, by using the aqueous alkali, the exo-hydroxyl group of isosorbide could be alkylated first, leaving the endo-hydroxyl group of two isosorbide molecules being linked with one epoxide. The bisisosorbide diglycidyl ether was prepared by heating the isosorbide with 50% sodium hydroxide solution and a large excess of epichlorhydrin, which was used to azeotrope away the water. Two equivalents isosorbide are linked by three molecules of epichlohydrin to form the epoxide dimer (Feng, 2010).

3.4.8.3 Toxicology and Human Health Evaluation

For isosorbide, the most widely available dianhydrohexitol, the hydroxyl group at C-2 is exo and that at C-5 is endo. Since it is classified by the Food and Drug Administration as a “generally recognized as safe,” GRAS, material and can be made readily available Isosorbide has potential for use as a “green” alternative to petroleum based chemicals and polymers (Feng, 2010).

As a biodegradable and naturally derived material, isosorbide is a rigid organic diol with the similar structure to that of BPA, but without the endocrine disrupting effect. Isosorbide can be attached to glycidyl ether or allyl ether to make crosslinkable epoxy resin monomer with similar properties to bis-A diglycidyl ether.

According to Michael Jaffe, Ph.D., development of the isosorbide/sorbitol is considered a GRAS material. The material is in current use as a component of cosmetics and pharmaceuticals, such as an angina drug. Toxicity testing as a food contact material is ongoing currently, with results expected over the next year. Expected associated toxicity is very low as a glucose-derived substance (Michael Jaffe, personal communication, 10-5-12).

Polypropylene melts above 266 degrees F. Above this temperature, it is possible for some antioxidant additives to breakdown and be released. The toxicity associated with the breakdown products has not been established. Exposures of this kind are not expected in the consumer marketplace (Beach, 2010).

3.4.8.4 Environmental Evaluation

Isosorbide, as a corn-based starch/sugar, is not expected to have any significant environmental or ecological toxic properties, according to Dr. Jaffe (Personal communication, 10-5-12). Specific food product-based testing whereby inferences may be made relative to ecological evaluations is on-going to verify these expectations.

3.4.8.5 US Patent Information

Example patent, thermoset epoxy polymers from renewable resources:

Patent Abstract

Novel thermoset epoxy polymers using the bisglycidyl ethers of anhydrosugars, such as isosorbide, isomannide, and isoidide, are disclosed. The bisglycidyl ethers are useful as substitutes for bisphenol A in the manufacture of thermoset epoxy ethers. The anhydrosugars are derived from renewable sources and the bisglycidyl ethers are not xenoestrogenic and the thermoset curing agents are likewise derived from renewable resources.

Inventors:	East; Anthony; (Madison, NJ) ; Jaffe; Michael; (Maplewood, NJ) ; Zhang; Yi; (Harrison, NJ) ; Catalani; Luiz H.; (Carapicuiba, BR)
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3.4.8.6 Advantages and Disadvantages to Use

3.4.8.6.1 Production Cost

A challenge for implementation of isosorbide-based epoxies is the simple commercialization of the product. At the time of report production, little information was available as to the ready availability of the product as a proprietary, patented material or the associated costs. It is unknown whether the infrastructure exists at this point in time to make production an economically viable and attractive option to canners and the greater manufacturing industry.

Production costs are unknown at this time, but costs are expected to be higher than BPA, a relatively inexpensive-to- produce chemical. In an assessment of material costs, the isosorbide ether is expected to (conservatively) cost in the range of not more than $2/lb., compared to approximately $0.50/lb for BPA.

3.4.8.6.2 Rigidity/Flexibility

When bisisosorbide diglycidyl ether was cured with an aliphatic amine, Jeffamine T403, a "green" commercial liquid curing agent, the tensile strength of the resulting isosorbide epoxy is 104% of the thermoset obtained from EPON 826, a diglycidyl ether of bisphenol A (DGEBA) type commercial epoxy resin (Feng, 2010). The impact strength of isosorbide epoxy is 40% higher than the Bis-A epoxy. The good mechanical properties of Jeffamine cured isosorbide epoxy provides a new class of environmentally friendly thermosets, which could be used as can coatings, adhesives and composites.

Isosorbide is expected to have very similar physical properties for use as a can lining agent as BPA, with an expectation of microwavabilty and dishwasher resistance, According to Michael Jaffe (personal communication, 10-05-12).

3.4.8.6.3 Durability

With different hardening agents, the pure isosorbide epoxy resin can be converted from the thermoplastic state to tough, hard, thermosets. Using the primary and secondary amines or anhydrides as hardeners for different crosslinking applications, a broad range of isosorbide derived epoxys can be made with properties such as excellent adhesion, high chemical or heat resistance and good-to-excellent mechanical properties.

Isosorbide is expected to have very similar physical properties for use as a can lining agent as BPA, with an expectation of

microwaveabilty and dishwasher resistance, according to Dr. Jaffe (personal communication, 10-05-12).

3.4.8.6.4 Weight Characteristics

Weight, as it applied to metal can linings, is not a factor for the isosorbide-based epoxies. There is no appreciable weight difference between applied isosorbide-based epoxies and BPA.

3.4.8.6.5 Shelf Life

Isosorbide is expected to have very similar physical properties for use as a can lining agent as BPA, with an expectation of similar properties to support adequate food safety and shelf-life, according to Dr. Jaffe (personal communication, 10-05-12).

3.4.8.6.6 Reactivity

Incorporation of isosorbide into a plastic polymer like PET on a commercial scale has encountered several problems. The secondary hydroxyl groups of isosorbide make it less reactive than the primary hydroxyls of ethylene glycol (Feng, 2010). This fact, coupled with the volatility of isosorbide, makes it difficult to get high incorporation into (polyethylene isosorbide terephthalate) PEIT copolymers and leads to complications with the recycle of the ethylene glycol/isosorbide stream generated during polymerization (Feng, 2010). Additionally, the stereochemistry of isosorbide is such that one OH is endo and one exo: this leads to a pronounced differential reactivity and an overall sluggishness in copolyester formations (Feng, 2010). Usually, only 35-50% of the added isosorbide becomes part of the polymer structure – the rest is lost by evaporation in the high vacuum stage of the polymerization reaction (Feng, 2010).

There are additional considerations regarding implementation as a can lining that could replace BPA. Isosorbide's glass transition temperature, measured by DSC as the typical step change in the heat flow curve, was shown to be 48℃, which is much lower than BPA-base epoxy of 90℃ (Feng, 2010). The depressed Tg relates to isosorbide's high affinity for water. When different crosslinkers were used to cure isosorbide epoxy resin, the more hydrophobic crosslinking agents like 4,4′-(hexafluoro-isopropylidene) diphthalic anhydride with higher crosslinking density were sufficient to offset the hydrophilic property of isosorbide glycidyl ether to raise its Tg to 200℃ (Feng, 2010). The water uptake ratio is believed to be determined by the factors of crosslinking density, the chemistry of crosslinking agent and the amount of free

hydroxyl groups on the backbone of the epoxy (Feng, 2010). By adding the hydrophobic functional group into the backbone of isosorbide epoxy or adjusting the amount and type of crosslinker, the mechanical property and water uptake ratio of the isosorbide derived epoxy could be optimized for different applications (Feng, 2010).

The low water uptake version of the isosorbide epoxy, with strong mechanical properties, is a viable candidate of use as can coatings and other industrial additives and adhesives.

3.4.8.6.7 Product Sealing and Reuse

Isosorbide Diglycidyl Ether is expected to have very similar physical properties to BPA, including the potential to reseal and reuse consumer containers.

3.4.8.6.8 End of Life Considerations

Unknown at this time.

3.4.8.7 Benchmark Scores

Chemicals such as isosorbide and its isomers, as sugar-derived dianhydrohexitols, are generally considered as inherently safe (GRAS materials). In light of available toxicity information, a GreenScreen score was not considered relevant.

3.4.8.8 State of Maine List Status

Isosorbide is not listed on the State of Maine Chemicals of Concern List.

3.4.9 Aseptic Cartons (e.g., Tetra Pak)

3.4.9.1 Chemical Overview

Aseptic cartons consist of paper (about 70% of package), LDPE (24%) and aluminum foil (6%). Due to the aseptic packaging process, a "higher quality product" is manufactured (APS 2010; Reuter 1993), with the packaging process offering a higher degree of disinfection (i.e., more sterile). Aseptic packaging does not contain any chemicals of concern identified by the State of Maine.

3.4.9.2 Product Markets and Function

Aseptic cartons are an alternative packaging product widely used in the U.S. for juice, soups, liquid dairy products and wine (BCF 2010). Tetra Pak is an industry leader in aseptic container production.

3.4.9.3 Human Health and Toxicology Evaluation

There are no significant human health/toxicology considerations associated with the paper and foil components of aseptic cartons. Health and toxicology considerations associated with LDPE are discussed in Section 3.4.2.3.

3.4.9.4 Environmental Evaluation

Seventy-five percent of the materials used in typical aseptic cartons are from renewable resources. Recycling options need to improve to further decrease the end-of-life impact on the environment. Approximately 70% of the renewable resources are wood and paper products. An assessment of the impact to the environment from paper production is outside the scope of this review.

3.4.9.5 US Patent Information

There are numerous patents that have been awarded to various companies in the production of aseptic cartons. Production of aseptic cartons and sale in the marketplace is dominated by a set of proprietary containers as manufactured by entities such as:

Amcor Limited
Aseptic Solutions USA
Baxter International Incorporated
Becton, Dickinson and Company
Bemis Company Incorporated
Bosch (Robert) GmbH
Catalent Pharma Solutions Incorporated
CDF Corporation
Cheer Pack North America, see CDF
Cryovac, see Sealed Air
Curwood, see Bemis
DuPont (EI) de Nemours
Fres-co System USA, see Goglio
GEA Group AG
Goglio SpA
Graham Packaging Holdings, see Reynolds Group Holdings
Horizon Pharmaceuticals Incorporated
International Dispensing Corporation
KHS, see Salzgitter
Kloeckner-Werke, see Salzgitter
Krones AG
Nestlé SA
OYSTAR Holding GmbH
Parish Manufacturing Incorporated
Printpack Incorporated
ProAseptic Technologies SL, see Sealed Air
Rapak, see Smith (DS)
Reynolds Group Holdings Limited
rommelag ag

Salzgitter AG
Scholle Corporation
SCHOTT AG
Sealed Air Corporation
Serac Group
Shibuya Kogyo Company Limited
Sidel, see Tetra Laval International
SIG Combibloc Group, see Reynolds Group Holdings
Smith (DS) plc
Spartech Corporation
Stork Food and Dairy Systems BV
Tetra Laval International SA
Vetter Pharma-Fertigung GmbH & Company KG
Weiler Engineering Incorporated
West Pharmaceutical Services Incorporated
Winpak Portion Packaging

3.4.9.6 Advantages and Disadvantages

3.4.9.6.1 Production Cost

An advantage of aseptic cartons is that aseptic packaging provides cost savings via reduced energy consumption and low cost packages. For example, can sterilization requires 17.8 megajoules per kilogram (MJ/kg) and jar sterilization requires 21.4 MJ/kg. Alternatively, aseptic milk production, including package manufacturing, requires only 3.8 MJ/kg (Reuter 1993) for sterilization.

Packaging is not expensive because paper is the primary component of the aseptic carton; paper is inexpensive.

However, a disadvantage of aseptic cartons is that packaging machinery/equipment to manufacture this alternative are more technologically advanced and there is an increased threat of malfunction. This results in the potential for higher production costs.

However, aseptic packaging provides cost savings via reduced energy consumption and low cost packages. For example, can sterilization requires 17.8 megajoules per kilogram (MJ/kg) and jar sterilization requires 21.4 MJ/kg. Alternatively, aseptic milk production, including package manufacturing, requires only 3.8 MJ/kg (Reuter 1993) for sterilization.

3.4.9.6.2 Rigidity/Flexibility of Plastic

Aseptic cartons do contain plastic; LDPE is used as a sealing layer. The LDPE is flexible, but in combination with the paper and aluminum foil, contributes toward a more rigid product. While the product is rigid enough to serve its function, the packaging is still somewhat pliable.

3.4.9.6.3 Durability

A disadvantage of aseptic cartons is their pliable packaging, which is more vulnerable to damage during production and transport.

3.4.9.6.4 Weight Characteristics

Aseptic cartons are considered a lightweight option for packaging.

3.4.9.6.5 Shelf Life

Aseptic cartons offer extended shelf-life. See section 3.4.9.6.6 for additional discussion.

3.4.9.6.6 Reactivity

Aseptic packaging/processing differs from typical manufacturing in that the product and packaging material(s) are sterilized separately (APS 2010). Also, aseptic packaged items (such as milk) can be stored at room temperature (eliminates cold storage needs), making it a suitable selection for infant formula packaging.

A disadvantage of aseptic packaging is that it is not microwaveable due to the aluminum foil layer. Also, this type of packaging would not stand up to repeated dishwasher use. This BPA alternative is not biodegradable.

3.4.9.6.7 Product Sealing and Reuse

Aseptic cartons fitted with a plastic spout and twist cap can be closed and reopened. However, aseptic cartons are not easily reusable due to its pliable construction and the shape of the cartons themselves.

3.4.9.6.8 End of Life Considerations

Aseptic cartons are not readily recyclable; 35% of households (in 30 states) have access to participating recycling programs. Refer to Appendix A for end of life considerations.

3.4.9.7 Benchmark Scores

A GreenScreen analysis was not considered relevant as part of this review. The components which comprise aseptic packaging are not associated with any problematic constituents or ingredient. A plastic scorecard ranking is not applicable for this BPA alternative.

3.4.9.8 State of Maine List Status

None of the fundamental components (e.g., paper products, aluminum foil, and LDPE) associated with aseptic cartons are listed on the State of Maine Chemicals of Concern List.

3.4.10 Laminated Pouches (e.g., Cheer Pack)

3.4.10.1 Chemical Overview

Laminated pouches such as Cheer Packs are made using 3-4 layers of laminate material, including an outer layer of glossy polyester, a barrier layer, a nylon layer to increase strength, and a sealing layer of PE or PP. Laminated pouches do not contain any chemicals of concern identified by the State of Maine.

3.4.10.2 Product Markets and Function

The typical markets for Cheer Pack application include energy drinks, beverages, yogurt, and sorbet. Other markets include cosmetics, gels, inks, shampoos, lotions and creams (Cheer Pack 2012).

3.4.10.3 Human Health and Toxicology Evaluation

Please refer to Sections 3.4.1 and 3.4.2 for a discussion of the human health implications of PP and PE as food contact layers for use in packaging.

3.4.10.4 Environmental Evaluation

Please refer to Sections 3.4.1 and 3.4.2 for a discussion of the environmental implications of PP and PE for use as food contact layers in packaging.

According to on-line Fres-co System USA information, laminated pouches offer an overall 40% reduction in packaging costs as compared with rigid plastic containers.

Production of laminated pouches are associated with a 62% reduction in GHG as compared with the production of rigid plastic containers, such as PE, according to on-line Fres-co System USA materials (http://www.fresco.com).

3.4.10.5 US Patent Information

Manufacture of laminated pouches is largely governed by US Patents. For example, Cheer Pack laminated pouches are currently manufactured under U.S. Patent # US D547,657 S

3.4.10.6 Advantages and Disadvantages

3.4.10.6.1 Production Cost

Production of laminated pouches is associated with a reduction in energy costs of 71% (BTU consumption), as compared with production of rigid plastic containers such as polyethylene according to on-line Fres-co System USA materials (http://www.fresco.com).

3.4.10.6.2 Rigidity/Flexibility of Plastic

Laminated pouches offer several advantages, including a flat, light-weight construction which results in a reduction of greenhouse gases produced from shipping.

3.4.10.6.3 Durability

An advantage of laminated pouches is that they are easy to use and can be used "on the go."

However, laminated pouches may be punctured. Care during shipping and handling is necessary to ensure that pouches are not punctured.

3.4.10.6.4 Weight Characteristics

Laminated pouches are very lightweight, offering 93% less packaging weight than glass containers and 39% less packaging weight than PET bottles.

3.4.10.6.5 Shelf Life

Laminated pouches are well-sealed and offer extended shelf life.

3.4.10.6.6 Reactivity

Laminated pouches utilize PE or PP as a non-reactive food contact layer.

However, this BPA alternative is not microwaveable and dishwasher use is not applicable. Also, laminated pouches are not biodegradable.

3.4.10.6.7 Product Sealing and Reuse

Another advantage is that most pouches are re-sealable (Cheer Pack 2012). However, laminated pouches are not considered reusable.

3.4.10.6.8 End of Life Considerations

Laminated pouches are not considered readily recyclable, but the caps (on applicable products) are made from HDPE and can be recycled. Further, laminated pouches produce less waste by volume: glass containers result in 14 times more landfill material by weight, per 100 grams (g) of product (on-line Fres-co System marketing materials). Laminated pouches result in 50% less landfill waste when compared to similar volume rigid plastic containers (that are not recycled) (on-line Fres-co System marketing materials). Refer to Appendix A for a summary of end of life considerations.

3.4.10.7 Benchmark Scores

A GreenScreen analysis is not applicable for the components (e.g., polyester, aluminum foil and PE or PP) of laminated pouches for the purpose of this analysis/comparative review – all are generally regarded as safe (GRAS) materials. A plastic scorecard ranking is not applicable for this BPA alternative.

3.4.10.8 State of Maine List Status

None of the fundamental components (e.g., polyester, aluminum foil and PE or PP) associated with laminated pouches are listed on the State of Maine Chemicals of Concern List.

Table 3-1: Research and Development, the Current Barriers to Entry into the Marketplace, the Projected Timeframe for Introduction of the Alternative into the Marketplace, and Advantages and Disadvantages of Using the Alternative in Lieu of the BPA-Product

Available/Emerging BPA Alternative	Research and Development	Barriers to Entry	Timeframe for Introduction	Advantages and Disadvantages
PP containers	Currently available	None PP is classified as # 5 plastic.	Currently used to package infant formula (e.g., Abbott) and food (e.g., Groupe Danone's YoBaby line uses both PP and PLA plastic containers).	While PP is recyclable, not all recycling centers will accept PP. PP passed both of Pure Strategies' screens for Human Health and Environment and Chemicals of High Concern. PP containers do not contain any Chemicals of Concern identified by the State of Maine.
PE containers	Currently available	None PE is a component of #1, #2, and # 3 plastics.	Currently used to package baby food (e.g., PE and PS layered plastic is used by Nestlé Gerber in their line of Gerber Organics baby food).	PE containers are a preferred alternative to infant formula cans lined with BPA, and they are easily recycled. Neither PE nor its constituent chemicals are Chemicals of High Concern, according to Pure Strategies, Inc. Assumption of health safety defined by their exclusion from the list. PE containers do not contain any Chemicals of Concern identified by the State of Maine.
PLA containers	Currently available	Classified as #7 plastic, though PLA is technically not recyclable but can be compostable.	Currently used to package baby food (e.g., Groupe Danone's YoBaby line uses both PP and PLA plastic containers).	PLA containers and/or linings are a preferred alternative to BPA infant products. However, they are not readily recyclable, but are compostable. PLA containers do not contain any Chemicals of Concern identified by the State of Maine.
PS containers	Currently available	None PS is classified as # 6 plastic.	Currently used as the outer layer in plastics for baby food (e.g., Nestlé Gerber).	It is readily recyclable, but is not preferred as a contact layer due to leachability of styrene from plastic into food. May be used as an outer layer in layered plastics in baby food products. PS containers contain

Available/Emerging BPA Alternative	Research and Development	Barriers to Entry	Timeframe for Introduction	Advantages and Disadvantages
				styrene which is classified as a carcinogen. PS should not be used as a contact layer.
Tritan Copolyester™	Currently available Eastman Chemical and independent testing have reportedly demonstrated that Tritan is free of estrogenic and androgenic activity.	Classified as #7 plastic, however, it is relatively new to the market and is not readily recyclable. In addition, this product is under patent and may not be cost-effective to mass produce at this point in time.	Currently in limited use to replace PC plastics.	Not a likely replacement for infant BPA-products. It replaces PC as a reusable plastic and is still being developed. Not readily recyclable.
Glass jars: lids with polyester coating (e.g., DAREX Polyester, Crown Cork and Seal polyester seal/coating)	Currently available	More expensive. Increased transparency is needed for the polyester coating options.	Currently used to package baby food, polyester with "melamine" is currently used as a lid coating (e.g., Initiative Foods Wild Harvest uses Crown Cork and Seal Technology).	Cost may be a disadvantage. Increased transparency needed about polyester compositions used. Glass jars with polyester coated lids do not contain any Chemicals of Concern identified by the State of Maine.
Cans lined with baked-on resins such as Oleoresin	Currently available Oleoresin is a natural mixture of oil and a resin extracted from various plants, such as pine or balsam fir. Oleoresin is currently used as can liner low acid foods (e.g., Eden Foods).	Increased transparency about the technology of oleoresin linings is needed to fully evaluate the environmental safety of this product.	Currently used as a can liner for highly acidic foods (e.g., Ball Corporation, Eden Foods).	Full disclosure of the technology is necessary. BPA-free cans and lids with BPA-free coatings are more expensive. Cans lined with baked-on resins do not contain any Chemicals of Concern identified by the State of Maine.
Isosorbide diglycidyl ether coatings	Undergoing research and development by New Jersey Institute of Technology (NJIT). Chemical is derived from corn-based isosorbide diglycidyl either. Both components of the epoxy – the resin and the hardener 0 are from water-soluble plant-derived chemistries.	More research is needed.	Patent received in 2008 by NJIT Research Professor. Unknown if/when the chemical will go into high volume production.	More research is needed.

Available/Emerging BPA Alternative	Research and Development	Barriers to Entry	Timeframe for Introduction	Advantages and Disadvantages
Aseptic cartons	Currently available	Available (e.g., Tetra Pak), however, aseptic cartons are not currently readily recycled. Aseptic cartons consist of several layers of paper (about 70% of the package), low density polyethylene (LDPE) (24%) and aluminum foil (6%), and the recycling infrastructure must evolve to accommodate access to carton recycling centers.	Currently used for liquid dairy products and other liquid products. Tetra Pak is a major manufacturer of aseptic packaging. It is unknown when aseptic cartons may be used for infant formula.	Aseptic containers and paperboard are a preferred option over aluminum or steel cans for infant formula packaging. While aseptic containers/cartons are not readily recycled currently, Tetra Pak, Elopak, Evergreen Packaging, SIG Combibloc and the Carton Council are working together to increase access to carton recycling to 60 million people in the US. In addition, aseptic cartons do not contain any Chemicals of Concern identified by the State of Maine.
Laminated pouches	Currently available	Available (e.g., Cheer Pak), however, laminated pouches are not readily recyclable at this time. Cheer Pack includes a polyester outer layer, aluminum foil and a PE or PP inner layer.	Currently used to package baby food (e.g., Hero Beech Nut and Hain Celestial Earth's Best uses Cheer Pack, Sprout Foods uses a laminated pouch as PP as the contact layer)	Not considered readily recyclable. In addition, laminated pouches do not contain any Chemicals of Concern identified by the State of Maine.

References: Guzman 2010

Table 3-2: Comparison of Advantages and Disadvantages of the Functionality of BPA Alternatives

Preferred BPA Alternative	Plastic Scorecard Overall Ranking	Advantages/ Features *	Disadvantages	Recycling Summary
PP containers	A – to F Note: With the use of safer additives and catalysts, and higher levels of post-consumer recycled PP content, PP could attain Grade A -.	Economical Heat Aging Resistance/Usable for hot food products and liquids High melting point (320°F) Light-weight Microwave/ Dishwasher Safe High Hardness/Stiffness Resistant to repetitive stress (e.g., repeated opening and closing of a lid) Good Processability Chemical Resistant This BPA alternative does not contain any chemicals of concern identified by the State of Maine. * advantages listed are for PPs manufactured for food containers	Degraded by UV light Flammable (retardant grades available) Attacked by chlorinated solvents and aromatics Difficult to bond Several metals accelerate oxidative degrading Low temperature impact strength is poor Limited recycling availability	Not all recycling centers will accept PP. Recycled PP is used to produce brooms, brushes, trays, rakes, bins, and pallets.
PE containers PET, HDPE, PE	C – to F * grade is specifically for PET Note: Antimony trioxide (a PET catalyst) is listed as a suspected carcinogen. This makes it a "red" chemical in the Green Screen rating system.	Low production costs Impact resistant Flexible Good Heat Seal Good Processability Recyclable Low Odor Mostly microwave safe (check labeling on individual products) This BPA alternative does not contain any chemicals of concern identified by the State of Maine. * advantages listed are for PEs manufactured for food packaging	High thermal expansion Poor weathering resistance Subject to stress cracking Difficult to bond Flammable Lower melting point (compared to PP) Low strength/stiffness Not all varieties are dishwasher safe	PE is easily recycled. Some varieties are widely accepted at recycling centers.

Preferred BPA Alternative	Plastic Scorecard Overall Ranking	Advantages/ Features *	Disadvantages	Recycling Summary
PLA containers	A – to F Note: With the use of safer additives and catalysts, and more sustainable agricultural practices PLA could attain Grade A -.	Renewable Resource Content; can contribute to reducing greenhouse gas emissions Biodegradable Compostable Heat resistant Production uses 65% less energy than producing conventional plastics Does not emit toxic fumes during incineration This BPA alternative does not contain any chemicals of concern identified by the State of Maine.	Low melting point; recommended storage temperature less than 105°F (ideal for cold storage or ambient temperature products) Requires a controlled composting environment (only currently 113 facilities currently in US and only ¼ accept residential collections from municipalities); still takes approximately 90 days to compost. Reportedly, large amounts of PLA could interfere with industrial composting, PLA reverts to lactic acid, making the compost wetter and more acidic, which will require a higher oxygen load for the microbes Requires segregation from other recyclables Typically manufactured from genetically modified corn; environmental and human health risks associated with genetically altered corn are unknown Not microwave safe	Not readily recyclable, but are compostable in controlled environments.
PS containers	Not Scored	Low production costs Light-weight Good insulator High Stiffness Heat Resistant Impact Resistant	Negative public perception (e.g., carcinogens [i.e., styrene and benzene] used in production, greenhouse gas effects) Preferred as an outer layer, not coming in contact with food (requires a liner, such as PE) Not all variations are microwave safe Several bans against using disposable food packaging containing PS Flammable (retardant grades available) Poor solvent resistance, attacked by many chemicals Homopolymers are brittle Subject to stress and environmental cracking Poor thermal stability	It is readily recyclable; limited recycling centers accept PS

Preferred BPA Alternative	Plastic Scorecard Overall Ranking	Advantages/ Features *	Disadvantages	Recycling Summary
Tritan Copolyester™ (Eastman Chemical)	Not Scored	Tough Heat Resistant Chemical Resistant Impact Resistant Easy processing Long product life Dishwasher durable * advantages listed are primarily for Eastman Tritan™ Copolyester EX401 developed for infant care products	Currently in limited use to replace PC plastics Mass production may not be cost effective Not currently available in disposable/one-time use products Compounds have not been tested for environmental impacts	Not readily recyclable
Glass jars: lids with polyester coating (e.g., DAREX Polyester, Crown Cork and Seal polyester seal/coating)	N/A	Polyester coating either replaces the need for BPA or is used as an additional coating, which reduces BPA leaching into food or beverage by 95% Glass jars with polyester coated lids do not contain any chemicals of concern identified by the State of Maine.	Expensive	Lids are not readily recyclable
Cans lined with baked-on resins such as Oleoresin	N/A	Previously used by Ball Corp. (proven technology) to manufacture cans prior to BPA's introduction to the market place and currently used with at least one manufacturer, Eden Foods. This BPA alternative does not contain any chemicals of concern identified by the State of Maine.	Costs on average 20% more (varies on size) to produce cans than BPA-lined cans Limited information on Oleoresin technology is available	N/A
Isosorbide diglycidyl ether coatings	N/A	Renewable resource Can be readily available at competitive pricing This BPA alternative does not contain any chemicals of concern identified by the State of Maine.	Unknown if/when the chemical will go into high volume production Additional research required to fully assess chemical and its human health and environmental impacts	Not in production.
Aseptic cartons	N/A	Aseptic packaged items (such as milk) can be stored at room temperature (eliminates cold storage needs) making it suitable selection for infant formula packaging Lightweight materials can be used Paper (main component) is inexpensive Extended shelf-life Packaging process uses less energy	Packaging more susceptible to damage Not microwave safe (aluminum foil layer) Packaging machinery/equipment more technologically advanced – increases threat of malfunction (i.e., higher costs)	Not readily recyclable; 35% of households (in 30 states) have access to participating recycling programs.

		Higher quality product Aseptic packaging does not contain any chemicals of concern identified by the State of Maine.		
Laminated pouches	N/A	Currently used in baby and children's food market Reduce packaging materials Light-weight Easy to use; on-the-go Although not recyclable, packaging is relatively small and compactable, having less impact on landfills Resealable packaging Laminated pouches do not contain any chemicals of concern identified by the State of Maine.	Not microwave safe	Not considered readily recyclable Caps (on applicable products) are made from HDPE and can be recycled

N/A – Not applicable.

4.0 Conclusions

In a review of the functionality and health considerations of alternatives, the AAR did not identify a readily available chemical alternative to replace BPA under its current model of use. In light of this, the AAR assesses alternative packaging options currently available in the marketplace and considers options under development, which may present viable options in the future.

Overall, it is believed that polyethylene, in a number of different formulations, represents the preferred choice in alternative packaging to replace containers that employ a BPA-based lining. Polyethylene is unreactive, stable and inexpensive. There are no health implications associated with polyethylene's use as a food packaging alternative and the compound's widespread use and recyclability tip the overall scales in favor of this compound as the (likely) preferred infant formula and baby food container-based packaging option when compared with other alternatives having no significant human health considerations.

The health implications associated with BPA exposure addressed in the attached AAR and in Appendix B, specifically (i.e., the GreenScreen for BPA), discuss any and all potentially adverse health effects associated with BPA via any investigated and documented route of exposure. The discussion of associated health effects is not limited to a particular dose range, constituent delivery mechanism (e.g., inhalation, ingestion, ingestion), or receptor population (e.g., fetus, infant, adult). Because the focus of the AAR is on infant formula and baby foodstuffs, a targeted human health assessment focused on dose and route of exposure is the more appropriate metric to underpin administrative authority decisions limited to actual or expected health risk for the targeted populations. Utilization of USEPA's Integrated Risk Information System (IRIS)-promulgated oral reference dose (RfD_o), could underpin an exposure assessment specific to nursing infants and babies predicated on ingestion of BPA-contaminated food – although it may require some adjustment (i.e., provisional RfD_o) to ensure hazards reflect the infant subpopulation and account for sensitive individuals. In its simplest form, this latter influence could be represented by an additional order-of-magnitude safety factor to account for sensitive populations (infants). Development of a Human Health Risk Assessment for BPA exposure to nursing infants and babies is beyond the scope of this assessment.

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Appendix A

End of Life Evaluation

With the increasing use of plastics in everyday packaging, the ability to recycle these plastics is a rising concern for consumers and entities responsible for solid waste management programs. Most consumers can recycle certain plastics with relative ease through curbside or drop-off recycling programs offered by municipalities. A 2011 study by Moore Recycling Associates Inc. (MRA) found that in certain states, such as Maine, residents are specifically asked not to place PET/PETE (PETE (PET and PETE are both acronyms for polyethylene terephthalate) bottles into the curbside recycling program, but are encouraged to collect and redeem their PET bottles through the states' deposit programs (MRA, 2011a). The MRA studied the availability of municipal recycling programs and determined that 94% of the population has access to programs that accept PETE (#1) and high density polyethylene (HDPE) (#2) bottles, and approximately 65% has access to programs that recycle polyvinyl chloride (PVC) (#3), low density polyethylene (LDPE) (#4), and polypropylene (PP) (#5) bottles. However, these percentages decrease to approximately half of the population for non-bottle rigid plastics (e.g., household containers, tubs, and lids), and 42.9% of the population has access to programs that recycle non-bottle rigid polystyrene (PS) (#6) plastic. The study also indicates that less than half (40%) of the U.S. population has access to programs that accept all types of plastic bottles, caps, and non-bottle rigid containers (MRA, 2011a).

The prevalence of PET/PETE and HDPE plastic bottle recycling programs may be due to the relative abundance of these materials. According to a report published by the American Chemistry Council (ACC), PETE and HDPE are the most common plastics used for bottles, comprising 96.5% of the U.S. plastic bottle market, and the percentage of PETE and HDPE plastic bottles recycled is about 29%. However, lower recycling rates were reported for bottles made from plastics #3 through #7 (3.0% for PVC, 2.0%, for LDPE, and 14.1% for PP). The report indicates that the recyclability of these plastics is limited by the smaller volume of material made from these plastics, which makes collection and processing uneconomical (ACC and APPR, 2010).

However, the growing awareness of consumers and the increased non-bottle collection efforts by municipal recycling programs may increase the recyclability of these plastics. As reported by the ACC for 2009, recovered non-bottle rigid containers are more likely to be made of HDPE, PP, and other/mixed plastics. This study reported that HDPE was the largest component (34%) of the non-bottle rigid plastics recovered, but PP (27%) and other/mixed plastics (26%) were also large proportions, and recycling of these plastics was on the rise. It also noted that a bale of mixed plastics is considered more valuable if it contains greater percentages of HDPE, LDPE, and PP (MRA, 2011b).

Currently, there are movements in the private sector to collect plastics that are more difficult to recycle. For example, yogurt and sour cream containers are made from PP, which is not as widely accepted by recycling programs. The Massachusetts company Preserve developed a program called *Gimme 5* that collects PP rigid plastic containers for recycling. Collection centers are set up at participating retailers, or consumers can mail their plastic containers to Preserve. Other programs for dropping off PS (#6) and plastic bags (#4) for recycling have also been implemented (EDF, 2011).

PS containers are readily recyclable, but this material is not preferred as a food contact layer. PE may be used as an outer layer in layered plastics in baby food products. In addition, PE is easily

recycled and some varieties are widely accepted at recycling centers (Guzman 2010, National Workgroup for Safe Markets 2010, Pierce and Caliendo 2012, USDHHS 2012).

There is also a push to recycle aseptic containers from the manufacturers of cartons because they are not readily recyclable. Aseptic cartons consist of several layers of paper (about 70% of the package), low density polyethylene (LDPE) (24%) and aluminum foil (6%), and the recycling infrastructure must evolve to accommodate access to carton recycling centers (Guzman 2010, National Workgroup for Safe Markets 2010, Pierce and Caliendo 2012, USDHHS 2012). The Carton Council reports that over 35 million households are recycling cartons in 40 states (Carton Council, 2011a), including the State of Maine. Tetra Pak, a member of the Carton Council, manufactures aseptic cartons for milk, juice, and other liquids. Tetra Pak describes its lightweight cartons as efficient, because they are made mostly from paper and are compact and recyclable (Tetra Pak, 2012). Tetra Pak reported in 2011 that more than 30% of the U.S. population has access to recycling programs that accept cartons, and set a goal for the year to increase this percentage to 35%. In 2010, Tetra Pak added 15 new sorting facilities in the U.S. and seven new domestic paper mills that recycle the carton fibers (Tetra Pak, 2011). The cartons are recycled into tissue products and other types of materials, and a new facility in Quebec breaks down cartons and other plastics and films into resin for flower pots, railway ties, and more (Tetra Pak, 2011). While aseptic containers/cartons are not readily recycled currently, Tetra Pak, Elopak, Evergreen Packaging, SIG Combibloc and the Carton Council are working together to increase access to carton recycling to 60 million people in the US. In addition, aseptic cartons do not contain any Chemicals of Concern identified by the State of Maine (Guzman 2010, National Workgroup for Safe Markets 2010, Pierce and Caliendo 2012, USDHHS 2012).

Certain materials remain difficult to recycle due to the recent development of the product and limitations in recycling technology. Both polylactic acid (PLA) and Eastman Chemical's Tritan copolyester are designated as #7 (other) plastics. One large disadvantage to PLA is the time and process it takes to biodegrade. Although PLA is biodegradable, unless in a "controlled composting environment," such as an industrial composting facility, a PLA bottle could take between 100 and 1,000 years to decompose in a typical landfill where it gets no light and a limited oxygen supply. An industrial composting facility heats PLA to 140 degrees Fahrenheit (°F) and feeds it a steady diet of digestive microbes (West 2012). Further, because PLA is not recyclable in the traditional sense, it must be separated from the recycling stream so as not to contaminate the other recyclables that are usually collected, baled, and sold. Once separated, NatureWorks LLC will buy back PLA from recycle centers and haul it to an industrial composter or return it to their facility for reuse. The NatureWorks LLC "Buy Back" program is currently active (NatureWorks LLC, 2012).

The Cheer Pack, a laminated pouch composed of PP, aluminum, and polyester, does not appear to be readily recyclable at this time, although its HDPE cap is recyclable. Not all recycling centers will accept PP. Recycled PP is used to produce brooms, brushes, trays, rakes, bins, and pallets and even clothing (e.g., Patagonia). Cheer Pack North America indicates that research and development is underway to create an additive that will make the film on the pouch environmentally degradable (Cheer Pack, 2010).

Layered plastics are designated #7 and have little recycling potential (CRG, 2006).

Containers lined with polylactic acid (PLA) are not recyclable; however, paper lined with PLA can be collected for large scale composting (Klink, 2011).

Plastic linings on aluminum and steel cans do not appear to be an issue, as recycling programs do not distinguish between lined and unlined cans (ecomaine, 2012; a non-profit waste management company owned and operated by 21 municipalities in Southern Maine).

The largest barrier to recycling materials appears to be the volume of material that can be recovered. PETE and HDPE are the most common plastics used for bottles, and these materials are the most widely recycled. Accordingly, a market is required for the recovered plastics, and the recycling facilities that sort material require a reliable supply of quality material (MRA, 2011b). For example, ecomaine does not accept Styrofoam, and indicates this is due to the lack of a Styrofoam market (ecomaine, 2012). Recent market prices of recovered plastics, in which recovered PS and PC have higher prices than PETE and HDPE, indicate the prices for PP appear more comparable. Overall, the recyclability of PP and other types of plastics appears to be growing and improving.

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Appendix B

GreenScreen for BPA

Green Screen Assessment Prepared By:
Name/Title: Travis R. Kline, MEM/Sr. Toxicologist
Mary C. Ruhter, MS/Toxicologist

GreenScreen Assessment for Bisphenol A *(CAS #80-05-7)*

GreenScreen Version 1.2

Note: Validation Has Not Been Performed on this GreenScreen Assessment

Chemical Name: Bisphenol A

Green Screen Assessment Prepared By:
Name: Travis R. Kline, MEM
Title: Sr. Toxicologist
Name: Mary C. Ruhter, MS
Title: Toxicologist
Organization: TechLaw, Inc.
Date: October, 2012

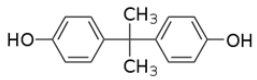
Quality Control Performed By:
Name: Adrian Nordone, PhD, DABT
Title: Sr. Product Regulatory Specialist
Organization: Senate Compliance Service Ltd.
Date: October, 2012

Chemical Name: Bisphenol A (CAS #80-05-7)

Also Called:
4,4'-isopropylidenediphenol; 2,2-bis(4-hydroxyphenyl)propane; bis(4-hydroxyphenyl) dimethylmethane; bis(4-hydroxyphenyl)propane; 4,4'-bisphenol a; DIAN; p,p'-dihydroxydiphenyldimethylmethane; p,p'-dihydroxydiphenylpropane; 2,2-(4,4-dihydroxydiphenyl)propane; 4,4'-dihydroxdiphenylpropane; 4,4'-dihydroxydiphenyl-2,2-propane; 4,4'-dihydroxy-2,2-diphenylpropane; dimethylmethylene-p,p'-diphenol; beta-di-p-hydroxyphenylpropane; dimethyl bis(p-hydroxyphenyl)methane; diphenylolpropane; 2,2-di(4-phenylol)propane; p,p'-isopropylidenebisphenol; 4,4'-dimethylmethylenediphenol; Phenol, 4,4'-(1-methylethylidene)bis-; 2,2-bis(4,4'-hydroxyphenyl)propane.

Chemical Structure(s):

$C_{15}H_{16}O_2$ or $(CH_3)_2C(C_6H_4OH)_2$



For Inorganic Chemicals and relevant particulate organics (*if not relevant, list NA*)
Define Properties:
1. Particle size (e.g. silica of respirable size) - *NA*
2. Structure (e.g. amorphous vs. crystalline) - *NA*
3. Mobility (e.g. Water solubility, volatility) - *NA*
4. Bioavailability - *NA*

Identify Applications/Functional Uses:
Bisphenol A is used primarily to make plastics, and products using bisphenol A-based plastics have been in commercial use since 1957. It is a key monomer in production of epoxy resins and in the most common form of polycarbonate plastic. Epoxy resins have many uses, including engineering applications such as electrical laminates for printed circuit boards, composites, paints and adhesives, as well as in a variety of protective coatings. Cured epoxy resins are used as protective liners in metal cans to maintain the quality of canned foods and beverages. Epoxy resins have been selected for protective coatings use in manufacturing based on the characteristics of toughness, adhesion, formability, and chemical resistance.

Historically, and with respect to infant formula cans and baby food jar lids, BPA-based epoxy resins have been used as a protective coating on the metal surfaces of food packaging. Infants and babies may be exposed to BPA when the chemical migrates from the coating on the metal into the food product.

Green Screen Rating[1]: BPA was assigned a Benchmark Score of [1] based on high toxicity ratings in Groups 1 and 2.

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated	single	repeated										
M	L	M	H	H	L	M	M	DG	DG	M	*L*	L	vH	H	L	L	vL	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values and lower confidence. Hazard levels in **BOLD** font reflect values based on test data (See Guidance).

Transformation Products and Ratings: Relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[2]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	On CPA Red List[3]?	Green Screen Rating[4]
End of Life	**Atmospheric (aerobic) breakdown**	2,3-bis(4-hydroxyphenyl)-1,2-propanediol	**139755-03-6**	**Not present on the Red List of Chemicals (CPA, 2011)**	**N/A**
End of Life	**Atmospheric (aerobic) breakdown**	p-hydroxyphenacyl alcohol	**5706-85-4**	**Not present on the Red List of Chemicals (CPA, 2011)**	**N/A**
End of Life	**Landfill (anaerobic) breakdown**	N/A (Does not readily breakdown under anaerobic conditions	**N/A**	**N/A**	**N/A**
End of Life	**Hydrolysis**	N/A (Does not readily breakdown due to a lack of functional groups that hydrolize)	**N/A**	**N/A**	**N/A**
End of Life	**Combustion**	Carbon monoxide	**630-08-0**	**Present on the Red List of Chemicals (CPA, 2011)**	**Reproductive and developmental toxicant, neurotoxicant (CPA, 2011)**
End of Life	**Combustion**	Carbon dioxide	**124-38-9**	**Not present on the Red List of Chemicals (CPA, 2011)**	**N/A**

[1] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[2] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

[3] The CPA "Red List" refers to chemicals: 1. flagged as Benchmark 1 using the GreenScreen™ List Translator or 2. flagged as Benchmark 1 or 2 using the GreenScreen™ List Translator and further assessed and assigned as Benchmark 1. The most recent version of the GreenScreen™ List Translator should be used.

[4] Conduct of assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

Introduction

BPA is an industrial chemical used to make a hard, clear plastic known as polycarbonate, which has been used in many consumer products, including reusable water bottles. BPA is also found in epoxy resins, which act as a protective lining on the inside of metal-based food and beverage cans. These uses of BPA are subject to premarket approval by FDA as indirect food additives or food contact substances. The original approvals were issued under FDA's food additive regulations and date from the 1960s.

Studies employing standardized toxicity tests used globally for regulatory decision making thus far have supported the safety of current low levels of human exposure to BPA. However, results of recent studies using novel approaches and different endpoints describe BPA effects in laboratory animals at very low doses corresponding to some estimated human exposures. Many of these new studies evaluated developmental or behavioral effects that are not typically assessed in standardized tests.

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction, part of the National Institutes of Health (NIH), completed a review of BPA in September 2008 (CERHR, 2008). The NTP uses five different terms to describe its level of concern about the different effects of chemicals: negligible concern, minimal concern, some concern, concern, and serious concern.

In its report on BPA, the NTP expressed "*some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A." The Program also expressed "*minimal concern* for effects on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current human exposures to bisphenol A" and "*negligible* concern" for other outcomes (CERHR, 2008).

The NTP does not make regulatory recommendations. With respect to neurological and developmental outcomes of BPA, the Program stated that "additional research is needed to more fully assess the functional, long-term impacts of exposures to bisphenol A on the developing brain and behavior" (CERHR, 2008).

Overall, the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health. Part of the difficulty for evaluating consistency lay in reconciling findings of different studies that use different experimental designs and different specific behavioral tests to measure the same dimension of behavior.

In August 2008, prior to the release of the final NTP report, FDA released a document entitled *Draft Assessment of Bisphenol A for Use in Food Contact Applications* (FDA, 2008a). This draft assessment was then reviewed by a Subcommittee of FDA's Science Board, which released its report at the end of October 2008 (FDA, 2008b).

Since that time, the Center for Food Safety and Applied Nutrition (CFSAN) within FDA has reviewed additional studies of low-dose toxicity cited by the National Toxicology Program and the Science Board Subcommittee, as well as other such studies that have become available. The Center then prepared a document entitled *Bisphenol A (CAS RN. 80-05): Review of Low Dose Studies,* dated August 31, 2009 (FDA, 2009). In the fall of 2009, FDA's Acting Chief Scientist asked five expert scientists from across the federal government to provide independent scientific evaluations of this document. In April 2010, FDA made the CFSAN documents available for public comment and also made public the independent scientific evaluations.

FDA is continuing to consider the low dose toxicity studies of BPA as well as other recent peer-reviewed studies related to BPA.

FDA's CFSAN and FDA's National Center for Toxicological Research has been and continues to pursue a set of studies on the exposure to dietary BPA and the safety of low doses of BPA, including assessment of the novel endpoints where concerns have been raised. These include studies pursued in collaboration with the NTP and with support and input from the National Institute for Environmental Health Sciences.

Recent evaluation by the FDA's CFSAN has:

- Determined that exposure to dietary BPA for infants, the population of most potential concern, is less than previously estimated. The initial FDA exposure estimates were 0.185 micrograms/kg-bw/day for adults and 2.42 micrograms/kg bw/day for infants. The new estimate of average dietary exposure, based on increased data collection, is 0.2-0.4 micrograms/kw-bw/day for infants and 0.1-0.2 micrograms/kg-bw/day for children and adults (CERHR, 2008).

Recent research studies pursued by FDA's National Center for Toxicological Research have (Doerge 2010a, 2010b, 2010c, 2011a, 2011b; Twaddle 2011; Fisher 2011):

- Found evidence in rodent studies that the level of the active form of BPA passed from expectant mothers to their unborn offspring, following oral exposure, is so low it could not be measured. The study orally dosed pregnant rodents with 100-1000 times more BPA than people are exposed to through food, and could not detect the active form of BPA in the fetus 8 hours after the mother's exposure.
- Demonstrated that oral BPA administration results in rapid metabolism of BPA to an inactive form. This results in much lower internal exposure of aglycone BPA (i.e., the active form) than that which occurs from other routes of exposure such as injection. Primates of all ages were also found to effectively metabolize BPA to its inactive form and excrete it much more rapidly and efficiently than rodents, thus reducing concerns about results from some rodent studies using oral and, particularly, non-oral exposures which result in higher actual internal exposures of rodents than of primates, including humans, exposed to the same dose.
- Developed a physiologically based pharmacokinetic model which can be used to predict the level of internal exposure to the active and inactive forms of BPA. This model allows comparisons of internal exposure across different ages and routes of exposure (e.g., oral and intravenous routes). Based on the effects of metabolism, internal exposures to aglycone BPA following oral administration are predicted to be below 1% or less of the total BPA level administered.

The following bullet points represent a synopsis of recent health effects documented in the primary literature and are excerpted from *An Update on the Recently Published Peer-Reviewed Scientific Literature on Bisphenol A (BPA)* (Vandenberg, 2012a):

- A 2009 study reported that prenatal exposure was associated with an increase in hyperactivity and aggression in two-year-old girls (Braun et al., 2009). In a follow-up assessment of this cohort of children, average maternal BPA levels were associated with an increase in anxiety and hyperactivity, and poorer emotional control and inhibition in three-year-old girls (Braun et al., 2011b). These results suggest that the behavior of BPA-exposed girls was masculinized. This developmental behavior result has been recorded in animal studies, which have indicated that BPA can masculinize behaviors of female rodents, and may feminize the behaviors of male rodents (Adewale et al., 2011; Patisaul et al., 2006; Patisaul et al., 2009; Rubin et al., 2006).

- Maternal BPA exposures may be associated with an increase in premature births (Cantonwine et al., 2010; Chou et al., 2011; Miao et al., 2011b). Maternal or paternal exposure to BPA during pregnancy was also associated with decreased anogenital distance in males (Miao et al., 2011a), suggesting feminization of male offspring. Maternal BPA levels also influenced newborn hormone levels that are associated with lipid metabolism (Chou et al., 2011). These results are consistent with a study in mice documenting disruption of glucose homeostasis in mothers and male offspring as a function of increased BPA exposure (Alonso-Magdalena et al., 2010b). Offspring may therefore be at risk for diabetes or obesity later in life.

- BPA exposure may also influence the developing immune system. Early prenatal exposure, but not later prenatal exposure or neonatal exposure, was associated with an increase in child wheeze at six months of age (Spanier et al., 2012). Additionally, BPA levels were associated with antibody titers to a common pathogen (cytomegalovirus), although the relationship was reversed for individuals younger vs. older than 18 years old (Clayton et al., 2011).

- Increased BPA levels are associated with decreased sperm quality following environmental (Meeker et al., 2010b) and occupational (Li et al., 2011) exposure. Higher BPA levels were also associated with poorer sexual function in occupationally or environmentally exposed men, including decreased sexual desire and decreased erection and orgasmic function (Li et al., 2010a; Li et al., 2010b). Several studies indicate that environmental exposures to BPA (i.e. those experienced by typical adults) affect testosterone levels in men (Galloway et al., 2010; Meeker, 2010; Mendiola et al., 2010), and are associated with changes in estrogenic gene expression in adult males (Melzer et al., 2011). In women receiving *in vitro* fertilization, higher BPA concentrations were associated with poorer oocyte quality, decreased estradiol levels, and decreased implantation success (Bloom et al., 2011; Ehrlich et al., 2012; Fujimoto et al., 2011; Mok-Lin et al., 2010).

- In 2008, the first study showing an association between urinary BPA levels and heart disease was published; individuals with higher BPA exposures were more likely to report cardiovascular diseases (Lang et al., 2008). In 2010, another cross-sectional study representative of the US population found that higher BPA levels were associated with an increased incidence of coronary heart disease (Melzer et al., 2010). This study was followed by a longitudinal study, in which BPA exposures were measured in adults free of coronary heart disease, and these individuals were then followed for 10.8 years (Melzer et al., 2012). Individuals with higher urinary BPA levels at time zero were more likely to develop coronary heart disease at the end of the study, compared to individuals with low urinary BPA concentrations at time zero. This study thus addresses the issue of causation, and suggests that BPA exposures could cause heart disease (and refutes the suggestion that heart disease causes increases in BPA exposure).

- However, BPA activates the human pregnane X receptor (Sui et al., 2012), which is involved in lipid homeostasis in addition to steroid and xenobiotic chemical metabolism. BPA may affect other endocrine parameters in addition to reproductive hormones and possibly metabolic homeostatis. Specifically, higher BPA levels were associated with decreased thyroid hormone levels in adults (Meeker et al., 2010a; Meeker and Ferguson, 2011).

- There is considerable evidence that BPA interferes with male and female reproduction, brain development, the adult brain, metabolic processes, and development of the mammary gland (Vandenberg et al., 2012b). Effects in numerous studies were observed at blood levels consistent with levels in humans in the general population (Vandenberg et al., 2007; vom Saal et al., 2007).

The FDA's National Center for Toxicological Research is continuing with additional studies, including:

- **Rodent subchronic studies** which are in progress to characterize potential effects, and, where observed, the dose-response relationship in the prostate and mammary glands for orally administered BPA. In addition, these studies will explore other issues, including potential effects of BPA on metabolic changes and cardiovascular endpoints. These studies will include an *in utero* phase, mimic bottle feeding in neonates, and employ a dose range that will cover the low doses where effects have been previously reported in some animal studies, as well as higher doses where estrogenic effects have been measured in guideline oral studies. Results from this study are expected to be available to FDA to inform the agency's decision-making, starting in 2012.

- **Rodent behavioral/neuroanatomical pilot studies** which are also already in progress as part of the sub-chronic study to characterize dose levels at which behavioral, neuroanatomical, neurochemical and hormonal endpoints may be affected by developmental exposure to BPA. These data are intended to evaluate possible effects of exposure to BPA during development that have been reported in some published studies on sexually dimorphic behavioral endpoints, such as anxiety, as well as on standard developmental neurotoxicity tests. Results from these studies are expected to be available to FDA to inform the agency's decision-making, starting in 2012.

Other Studies. Other studies on the safety of BPA are also underway. For example, the National Toxicology Program/Food and Drug Administration (NTP/FDA) will conduct a long-term toxicity study of BPA in rodents to assess a variety of endpoints, including novel endpoints where concerns have been raised. NTP/FDA will

collaborate with the National Institute of Environmental Health Sciences by providing animals and tissues to a consortium of researchers with interest in studying a variety of additional toxicological areas.

Infants. Infants are a potentially sensitive population for BPA because: (1) their neurological and endocrine systems are developing; and (2) their hepatic system for detoxification and elimination of such substances as BPA may be immature.

- **FDA is supporting the industry's actions to stop producing BPA-containing bottles and infant feeding cups for the U.S. market.** Major manufacturers of these products have stopped selling new BPA-containing bottles and infant feeding cups for the U.S. market. Glass and polypropylene bottles and plastic disposable "bag" liners have long been alternatives to polycarbonate nursing bottles.

- **FDA is facilitating the development of alternatives to BPA for the linings of infant formula cans.** FDA has already noted increased interest on the part of infant formula manufacturers to explore alternatives to BPA-containing can linings, and has received notifications for alternative packaging. The agency is supporting efforts to develop and use alternatives by: (1) working with manufacturers regarding the regulatory status and safety of alternative liners; (2) giving technical assistance to those wishing to prepare applications for approval of alternatives; and (3) expeditiously reviewing any such new applications for alternatives. Because reliable can lining materials are a critical factor in ensuring the quality of heat processed liquid infant formula, safe replacement of such materials requires not only that they both be safe for food contact but also allow for processing that is fully functional in protecting the safety and quality of the infant formula itself.

Summary:

BPA is a reproductive and developmental toxicant at doses in animal studies of ≥ 50 mg/kg-bw/day (delayed puberty in male and female rats and male mice); ≥ 235 mg/kg-bw/day (reduced fetal or birth weight or growth early in life, effects on testis of male rats); and ≥ 500 mg/kg-bw/day (possible decreased fertility in mice, altered estrous cycling in female rats, and reduced survival of fetuses). Systemic effects such as a reduction in body weight, changes in relative organ weights, and increases in liver toxicity were observed at doses above 5 mg/kg-bw/day (identified as a No-Observed-Adverse-Effect-Level [NOAEL] with a Low-Observed-Adverse-Effect-Level [LOAEL] of 50 mg/kg-bw-day) (USEPA 2010). Low-dose effects relate to endocrine disruption and include effects on puberty and developmental neurotoxicological effects on the brain and behavior at doses as low as 2 ug/kg-bw/day in animal studies (USEPA 2010).

Recent studies by the US Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) indicate that the latest estimate of average dietary exposure, based on increased data collection, is 0.2-0.4 mg/kg-bw/day for infants and 0.1-0.2 micrograms/kg-bw/day for children and adults (USDHHS 2012). However, there is controversy about impacts to human health even at very low-dose exposure.

Most studies of the health effects of BPA have focused on estrogenic activity because it is widely documented to function as an agonist of certain estrogen receptors (ERs) (Lee et al. 2003) and as an androgen antagonist and to suppress aromatase activity (Bonefeld-Jorgensen et al. 2007) (Melzer et al. 2011). Thyroid hormone disruption (Moriyama et al. 2002), altered pancreatic β-cell function (Ropero et al. 2008), and obesity-promoting effects (Newbold et al. 2008), have also been reported in research studies. Many of these effects are already detectable at intakes less than the current tolerable daily intake (TDI) of 0.05 mg/kg/day prompting concerns that the TDI should be revised (Melzer et al. 2011). However, there has not been a strong body of evidence that BPA at these low levels exerts significant and substantive biological effects in humans until recently. Melzer et al. 2011 found that BPA exposure is associated with *in vivo* estrogenic gene expression in adults and is associated with male infertility. Also, research performed by Braun et al. (2009) found an association between mean prenatal BPA concentrations and externalizing scores in females. Further, Rissman et al. (2012) found that low dose gestational exposure to BPA, a dose within the reported human levels, leads to trans-generational behavioral changes in mice, including increased anxiety, aggression and cognitive impairments for four generations (The Endocrine Society News Room 2012). The study by Rissman et al., *Gestational exposure to Bisphenol A produces trans-generational changes in behaviors and gene expression,* will appear in the August 2012 issue of *Endocrinology* (The Endocrine Society News Room 2012).

Table 1: BPA Intake Limits for Human Health Assessments (USEPA 2010)

Authors	Intake Limit (mg/kg/day)[1]	Endpoint (Animal dose in mg/kg/day) and Source
USEPA's Integrated Risk Information System (IRIS) (1993)	0.05	Reduced body weight (5) NTP 1982 two year cancer study in both rats and mice (as cited in USEPA 1993)
FDA (2008)	0.005	Systemic – reduced body wt and liver effects (5)
	0.05	Irreversible reproductive effects (50)
	0.5	Reversible reproductive effects (50) (All based on both 2-generation mouse study (Tyl et al., 2008) and 3-generation rat study (Tyl et al., 2002)
European Food and Safety Authority (EFSA) (2006, 2008a-b)	0.05	Used 5 (lowest value in cited studies) Tyl et al. (2002, 2008)
Japan (AIST, 2004)	0.05	Body weight (5) Tyl et al. (2002, 2008)
	0.5	Reproduction (50) Tyl et al. (2002, 2008)
Canada (2008)	Not reported	Body weight reduction (5) and developmental and reproductive effects (50), Tyl et al. (2002, 2008) Cited numerous studies with effect levels ranging from 0.010 to 0.100 mg/kg/day for a variety of effects in mice and/or rats including changes in: maternal behavior, gender-specific behaviors; sexual performance; novelty-seeking/impulse behaviors; avoidance response; maze performance.
Willhite et al. (2008) (NSF International)	0.016	Used 5 (lowest value in cited studies) Tyl et al. (2002, 2008)

1 Most risk assessments take an exposure value from an animal study (dose in mg/kg-bw/day) and divide it by several uncertainty factors to arrive at an acceptable dose in humans. This value is what is shown here as an "intake limit" and is what is compared to an expected/estimated exposure value in a risk assessment. The uncertainty factors used by the various assessments are: EPA (IRIS) – 1000; FDA – either 1000 (systemic or irreversible effects) or 100 (reversible effects); EFSA/EU – 100; Japan – either 100 or 500; Canada – did not specify; and NSF Int.'l – 300.

Report Organization:

1.0 Hazard Classification Summary Section:

1.1 Group I Human Health Effects (Group I Human)

- 1.1.1 Carcinogenicity
- 1.1.2 Mutagenicity/Genotoxicity
- 1.1.3 Reproductive Toxicity
- 1.1.4 Developmental Toxicity incl. Developmental Neurotoxicity
- 1.1.5 Endocrine Activity

1.2 Group II and II* Human Health Effects (Group II and II* Human)[5]

- 1.2.1 Acute Mammalian Toxicity
- 1.2.2 Systemic Toxicity/Organ Effects Including Immunotoxicity
- 1.2.3 Neurotoxicity
- 1.2.4 Skin Sensitization
- 1.2.5 Respiratory Sensitization
- 1.2.6 Skin Irritation/Corrosivity
- 1.2.7 Eye Irritation/Corrosivity

1.3 Ecotoxicity

- 1.3.1 Acute Aquatic Toxicity
- 1.3.2 Chronic Aquatic Toxicity

1.4 Environmental Fate

- 1.4.1 Persistence
- 1.4.2 Bioaccumulation

1.5 Physical Hazards

- 1.5.1 Reactivity
- 1.5.2 Flammability

2.0 References

Appendices:

- Appendix 1: EpiSuite Output - BPA
- Appendix 2: ECOSAR Output - BPA

[5] Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Benchmark Score for BPA:
BPA is a Benchmark 1 based on: High developmental toxicity and endocrine activity (i.e., High score for Group I Human).

1.0 Hazard Classification Summary Section:

1.1 Group I Human Health Effects (Group I Human)

1.1.1 Carcinogenicity (C) Score (H, M or L):
BPA was assigned a score of Moderate [M] for carcinogenicity based on a lack of carcinogenic classification under US EPA's IRIS Program (USEPA, 2012). BPA is not classified as carcinogenic on Authoritative or Screening Lists and professional judgment.

Authoritative and Screening Lists:

- BPA is not listed on Authoritative or Screening lists as a carcinogenic compound.

A concern for predisposition to carcinogenicity of the mammary and prostate glands has been suggested. The data reported in the literature are not adequate to draw any conclusions based on the nature of the endpoints examined, limitations in study designs, and the quality of the data. Available bioassay data, conducted in mice and rats by NTP, does not indicate a concern for this endpoint; however, the lack of an *in utero* exposure period in the NTP study is a limitation (FDA, 2008a).

BPA has not shown any significant carcinogenic activity in two standard oral cancer bioassays in rats and mice. This information principally concerns the potential promoting effects of prenatal and/or neonatal exposure of rats to BPA on the carcinogenesis induced by established carcinogens/initiators in specific organs (prostrate, uterus, thyroid, lungs, liver, thymus, esophagus, liver and mammary gland). One single study (Murray *et al*., 2007) examined the potential full carcinogenic activity of prenatal exposure to BPA on the mammary gland (ECJRC, 2010).

Three studies were conducted by the oral route of exposure and three by subcutaneous administration. Although not conclusive, the studies involving oral administration showed that BPA does not exert promoting activity up to relatively high levels of exposure on DMAB-induced prostate cancer (up to 120 mg/kg bw/day), ENNG-induced uterus cancer (up to 6 mg/kg bw/day) and BHP-induced thyroid, lung, liver, thymus and esophagus cancer (up to 400-600 mg/kg bw/day). The studies involving subcutaneous administration showed that BPA at relatively low doses (in the µg/kg bw/day range) does increase the incidence of E+T-induced preneoplastic and neoplastic lesions of the prostate and the incidence of NMU-induced hyperplastic lesions of the mammary gland and does induce hyperplastic and cribriform lesions of the mammary gland. However, these studies had several limitations and methodological weaknesses which make it difficult to establish whether the reported findings were real, treatment-related effects. Furthermore, because of the subcutaneous route of administration, it is questionable whether they are relevant to normal routes of exposures. Overall, there is only one recent study in which the full carcinogenic potential of BPA on the mammary gland has been examined in a prenatal model. Although this study claims that prenatal exposure to BPA induces preneoplastic and neoplastic lesions of the mammary gland, its validity is hampered by serious methodological limitations. It is also noted that these findings are inconsistent with the absence of preneoplastic lesions of the mammary gland in the offspring of several standard multi-generation studies in rats and mice. Regarding the other available studies, it can be concluded that prenatal and/or neonatal exposure to BPA does not exert promoting activity on the carcinogenesis induced by established carcinogens/initiators in specific organs (ECJRC, 2010).

While recent information on the potential carcinogenic and/or promoting effects of BPA in prenatal and neonatal rat models supports the conclusion that BPA does not possess any significant carcinogenic potential (ECJRC, 2010), carcinogenicity cannot be ruled out for further consideration. There is concern for carcinogenicity associated with endocrine-related mechanisms due to its estrogenic properties. Several non-guideline studies indicate proliferation of mammary ductal epithelium and squamous metaplasia of prostatic epithelium in offspring, conditions thought by many to predispose to neoplasia (FAO/WHO 2011). In response to the uncertainty, NTP and FDA are conducting a new GLP study that is designed to include a wide oral dosing range, to include pre-and perinatal exposures (FAO/WHO 2011). While data from guideline studies suggest low concern for cancer, there are non-guideline

studies that demonstrate evidence of proliferative lesions, carcinogenicity cannot be ruled out, leading to a designation of Medium in the Group 1 category for Carcinogenicity.

1.1.2 Mutagenicity/Genotoxicity (M) Score (H, M or L):
BPA was assigned a score of Low [L] for mutagenicity/genotoxicity based on: not classified as a mutagen.

Authoritative and Screening Lists:

- BPA is not listed on Authoritative or Screening lists as a mutagenic compound.

LOW: Based on determination by FAO/WHO (2011) that: (1) BPA is not a mutagen in *in vitro* test systems; (2) BPA does not induce cell transformation; and (3) *in vivo* evidence for BPA-induced clastogenic effects is inconsistent and inconclusive, although some *in vitro* studies have shown BPA to affect chromosomal structure in dividing cells. The conclusion of FAO/WHO (2011) is that BPA is not likely to pose a genotoxic hazard to humans.

No human data regarding mutagenicity are available. However, BPA appears to have demonstrated aneugenic potential *in vitro,* positive results being observed without metabolic activation in a micronucleus test in Chinese hamster V79 cells and in a non-conventional aneuploidy assay in cultured Syrian hamster embryo cells. Additionally, in cell-free and cellular systems, there is information that shows BPA disrupts microtubule formation. BPA has been shown to produce adduct spots in a post-labeling assay with isolated DNA and a peroxidase activation system, but it does not appear to produce either gene mutations or structural chromosome aberrations in bacteria, fungi or mammalian cells *in vitro*. However, some deficiencies in the conduct of these studies have been noted and the negative results cannot be taken as entirely conclusive. BPA does not appear to be anuegenic *in vivo.* A standard mouse bone marrow micronucleus test has given a negative result. BPA was negative in a briefly reported dominant lethal study in rats but, given the limited details provided, this is not regarded as an adequate negative result. The only other data in somatic cells *in vivo* are from a 32P-postlabelling assay, which showed that BPA is capable of producing DNA adduct spots in rat liver following oral administration. These adduct spots were not characterized fully (ECJRC, 2010).

Considering all of the available genotoxicity data, and the absence of significant tumor findings in animal carcinogenicity studies, it does not appear that BPA has significant mutagenic potential *in vivo*. Any aneugenic potential of BPA seems to be limited to *in vitro* test systems and is not of high concern. The relevance of the finding that BPA can produce rat hepatic DNA adduct spots in a post-labeling assay is not entirely clear. However, given the absence of positive results for gene mutation and clastogenicity in cultured mammalian cell tests, it seems unlikely that these are of concern for human health (ECJRC, 2010).

More recent information on the mutagenicity of BPA deals with the effects of short-term, low dose exposure to BPA on the meiotic processes of female mice during the final stages of oocyte growth. These new data have shown that BPA produces an increase in congression failure, a misalignment of chromosomes during the metaphase stages of meiosis II. However, in view of several methodological weaknesses and flaws identified in the study along with the reporting inadequacies, and taking into account the known mutagenicity and toxicological profile of BPA, these results cannot in themselves be taken as conclusive evidence of an effect of BPA on germ cell meiosis. Furthermore, these findings have not been confirmed in more recent publications (ECJRC, 2010).

Therefore, the conclusion is that BPA has no significant mutagenic potential *in vivo*, is still valid (ECJRC, 2010).

1.1.3 Reproductive Toxicity (R) Score (H, M, or L):
BPA was assigned a score of Moderate for reproductive toxicity based on: possible reproductive effects.

Authoritative and Screening Lists:

- BPA was listed as H361f by EC – CLP/GHS Hazard Statements (EU H-Statements) as BPA is suspected to damage fertility. This translates to a Moderate concern for reproductive toxicity.

- BPA carries an EU Risk Phrase of R62. This translates to Moderate concern for reproductive toxicity.

- BPA is classified by US NIH – Reproductive and Developmental Monographs (NTP-OHAaT) as Category B, some evidence of adverse reproductive toxicant effects. This translates to a Moderate concern for reproductive toxicity.

- BPA is classified by GHS Japan as Category 2, which translates to a Moderate concern for reproductive toxicity.

MODERATE: Based on NOAELs of 4.75 mg/kg bw-day and 47.5 mg/kg bw-day for reproductive toxicity in male and female rats, respectively. Conclusions of NTP-CERHR (2008) include sufficient evidence in rats and mice that subchronic or chronic oral exposures to bisphenol A causes female reproductive toxicity at doses ≥475 mg/kg bw-day (highest NOAEL = 47.5 mg/kg-day) and male reproductive toxicity at doses ≥47.5mg/kg bw-day (highest NOAEL = 4.75 mg/kg bw-day). There is considerable uncertainty regarding the results of recent studies that reported reproductive and/or developmental effects in laboratory animals administered BPA at oral doses <5 mg/kg bw-day.

BPA has been identified as a Category 2 Reproductive toxicant (Hazard statement: Suspected of damaging fertility) (ECJRC, 2008).

The effects of BPA on fertility and reproductive performance have been investigated in three good-quality studies: two generation and multi-generation studies in the rat, and a continuous breeding study in the mouse. Although no effect on fertility was seen in the rat two-generation study, low dose levels were employed (0.2-200 μg/kg/day). In the multi-generation study, an effect on fertility (reduction in litter size) was seen in all three generations at the top dose of 500 mg/kg. Although this effect was seen only at a dose level causing parental toxicity (a reduction in body weight gain (>13%) in both sexes and renal tubule degeneration in females only), it is not clear whether the finding could be a secondary consequence of parental toxicity, or a direct effect of BPA. In light of this uncertainty, and given that an adverse effect on fertility has been seen in the mouse, it is prudent to assume that BPA may be having a direct effect on fertility in this study. No effects on fertility were seen at 50 mg/kg (ECJRC, 2010).

FDA reviewed two studies concerning the reproductive toxicity of BPA in rodents: a two-generation reproductive toxicity study in CD-1® Swiss Mice and a three generation reproductive study in CD Sprague-Dawley rats (FDA, 2008a). These studies were chosen for full review based on their comprehensive dosing, adherence to accepted guidelines and inclusion of several additional endpoints. Pivotal aspects of the study review are included below.

Two-Generation Reproductive Toxicity Evaluation of Bisphenol A Administered in the Feed to CD-1® Swiss Mice (FDA, 2008a)

The study was conducted by RTI International, Research Triangle Park, NC and was sponsored by the American Plastics Council. The in-life portion of the study occurred in 2005 – 2007; the study report was finalized 03/01/2007. BPA was administered via feed to 9 groups of 6-week-old mice at doses of 0 (2 groups), 0.018, 0.18, 1.8, 30, 300, or 3500 ppm BPA (equivalent to intakes of 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg/kg bw/day, respectively). 17β-estradiol was used as a positive control and was administered at 0.5 ppm (intake of 0.08 mg/kg bw/day) to a separate group. F0 animals were exposed for eight weeks prior to mating, during the mating period, through gestation, and during the three-week lactation period. F1 offspring (28/sex/group) were exposed through premating, mating, gestation and lactation. F0 dams were necropsied after weaning occurred, F1 dams and F2 offspring were necropsied at the time of weaning F2 offspring. F0 and F1 males were necropsied at the end of the gestation of their respective F1 and F2 litters. In addition, one F1 male/litter was randomly selected at weaning for retention and treatment for three months. These animals were evaluated for andrology, necropsy, and histopathology concurrent with F1 parental males. (This resulted in an additional 21-27 *n* in BPA treatment groups and 50 in control.) Treatment-related effects at 3500 ppm included the following: decreased epididymal sperm concentration; decreased paired epididymal weights (did not achieve statistical significance) (F0 males); significantly reduced absolute paired epididymal weights (F1 males); significantly increased gestational length (F0 and F1 females); reduced pup body weight (PND 7 – 21, F1); reduced absolute and relative spleen weights (F1 and F2 weanlings); increased incidence of undescended testes, seminiferous tubule hypoplasia, and decreased testes weight (F1 and F2 male weanlings); delayed preputial separation (F1 male offspring); increased liver weights (absolute and relative), increased incidence in minimal to mild centrilobular hepatocyte hypertrophy, increased kidney weights (absolute and relative), increased minimal to mild nephropathy (F0 and F1 adults and retained F1 adult males); day of acquisition (vaginal patency) was statistically significantly accelerated when adjusted by body weight on PND 21 (F1 females only animals measured). Results at 300 ppm

included increased incidence in minimal to mild centrilobular hepatocyte hypertrophy (adult F0 males, retained F1 males and F1 females). FDA calculated the following NOAELs for the study:

- Systemic: 30 ppm (5 mg/kg bw/day)
- Reproductive: 300 ppm (50 mg/kg bw/day)
- Offspring: 300 ppm (50 mg/kg bw/day).

Three-Generation Reproductive Toxicity Evaluation of Bisphenol A in the Feed of CD® (Sprague-Dawley) Rat (FDA, 2008a).

The study was conducted by RTI International, Research Triangle Park, NC, and was sponsored by the Society of Plastics Industry. The in-life portion of the study occurred in 1998-2000; the study report was finalized 10/05/2000. BPA was administered via feed to CD-SD virgin rats (30/sex/dose) at doses of 0, 0.015, 0.3, 4.5, 75, 750, or 7500 ppm BPA (equivalent to intakes of 0, 0.001, 0.02, 0.3, 5, 50, or 500 mg/kg bw/day, respectively). F0 animals were exposed for 10 weeks prior to mating, during the mating period, through gestation, and during the lactation period until weaning (PND 21). F1 litters were culled to 10 pups (equal sex ratio) at PND4. F1 and F2 offspring (30/sex/group) were exposed through premating (13-15 weeks), mating, gestation and lactation. F0 males were sacrificed and necropsied after F1 delivery. F3 weanlings were sacrificed after approximately 10 weeks of continued dietary exposure. Treatment-related reproductive effects at 7500 ppm included reduced absolute paired ovarian weights (all females); reduced relative paired ovarian weights (F0, F1 and F2); increased paired ovarian primordial follicle counts (F0); reduction in number of implants, total and live pups per litter at birth (F1, F2, F3); reduction in epididymal sperm concentration (F1 males); decreased testicular homogenization-resistant spermatid head counts (DSP, F3 males). A reduction in number of implants total and live pups per litter at birth was also seen at 0.3 ppm for F3. Offspring effects included decreased pup body weights per litter during lactation (7500 ppm, F1, F2, and F3; 75 ppm and 4.5 ppm, F2), delayed absolute age of vaginal patency and delayed absolute age at preputial separation (7500 ppm, F1, F2 and F3). Systemic effects included reduced body weight and body weight gain (7500 ppm, F0, F1, F2, and F3); reduced body weight during gestation and lactation (7500 ppm, F0, F1 and F2 females); decreased terminal body weights (7500 ppm, all); increased slight to mild renal tubular degeneration and chronic hepatic inflammation (7500 ppm, F1 and F2 females); chronic hepatic inflammation (7500 ppm, F0 males); at 750 ppm, effects observed included reduced body weights during lactation (F1 females), reduced body weights during gestation and lactation (F0 and F2 females), and decreased terminal body weights [F1 (all) and F2 (males)]. An observation of increased anal genital distance was made only in F2 females, all doses except for 75 and 7500 ppm. This observation was considered sporadic based on the lack of dose response and lack of finding in F3 females and; therefore, was not considered treatment related. FDA calculated the following NOAELs for the study:

- Systemic: 75 ppm (5 mg/kg bw/day)
- Reproductive: 750 ppm (50 mg/kg bw/day)
- Offspring: 750 ppm (50 mg/kg bw/day).

An additional GLP study by Ema *et al.* (2001) reports developmental and reproductive toxicity of BPA in a 2-generation study in Crj:CD(SD) rats. Animals (25/sex/dose) were gavaged daily with 0, 0.2, 2, 20, 200 μg/kg bw/day BPA throughout premating, mating, gestation, and lactation. Stainless steel cages were used for housing. Bedding/diet (< 0.003 μg/g, LOD) and drinking water (0.03 μg/L) were analyzed for BPA. Endpoints included clinical observations, body weight, food consumption in F0, F1 and F2 generations; estrous cyclicity (adult females only in F0, F1 and F2); reproductive effects (parents/offspring-F0/F1 and F1/F2); developmental parameters (F1 and F2), behavioral effects (F1); necropsy and histopathology (F0, F1 and F2); organ weight; serum hormone levels (F0 and F1 adults; and sperm parameters (F0 and F1). Some statistically significant changes were observed; however, those changes were sporadic, inconsistent or non-dose-dependent and, accordingly findings were considered non-treatment-related. BPA exposure did not cause compound-related reproductive or developmental changes in this 2-generation rat study.

Based on the reviewed studies in rodents, the NOAEL for reproductive and offspring toxicity is 50 mg/kg bw/day in both rats and mice. A NOAEL for systemic toxicity was determined to be 5 mg/kg bw/day in both species.

Study:
Tyl, 2008. RTI International, Research Triangle Park, NC, (Study number 65C-09301.000.003/0209301.000.003); Title: Two-Generation Reproductive Toxicity Evaluation of Bisphenol A Administered in the Feed to CD-1® Swiss Mice.

BPA Dose: 3500 ppm
Dose Effects: F0 males: decreased epididymal sperm concentration; decreased paired epididymal weights (did not achieve statistical significance); F1 males: significantly reduced absolute paired epididymal weights; F0 and F1 females: significantly increased gestational length.
NOAEL/Comments: Systemic: 30 ppm (5 mg/kg bw/day) Reproductive: 300 ppm (50 mg/kg bw/day) Offspring: 300 ppm (50 mg/kg bw/day).

Study:
Tyl, 2002. RTI International, Research Triangle Park, NC. (Study number 65C-07036-000); Three-Generation Reproductive Toxicity Evaluation of Bisphenol A in the Feed of CD® (Sprague-Dawley) Rats.

BPA Dose: 7500 ppm
Dose Effects: All females: reduced absolute paired ovarian weights; F0, F1 and F2: reduced relative paired ovarian weights; F0: increased paired ovarian primordial follicle counts; F1, F2, F3: reduction in number of implants, total and live pups per litter at birth; F1 males: reduction in epididymal sperm concentration; F3 males: decreased testicular homogenization-resistant spermatid head counts (DSP).
NOAEL/Comments: Systemic: 75 ppm (5 mg/kg bw/day) Reproductive: 750 ppm (50 mg/kg bw/day) Offspring: 750 ppm (50 mg/kg bw/day).

Increased BPA levels are associated with decreased sperm quality following environmental (Meeker et al., 2010b) and occupational (Li et al., 2011) exposure. Higher BPA levels were also associated with poorer sexual function in occupationally or environmentally exposed men, including decreased sexual desire and decreased erection and orgasmic function (Li et al., 2010a; Li et al., 2010b). Several studies indicate that environmental exposures to BPA (i.e. those experienced by typical adults) affect testosterone levels in men (Galloway et al., 2010; Meeker, 2010; Mendiola et al., 2010), and are associated with changes in estrogenic gene expression in adult males (Melzer et al., 2011). In women receiving *in vitro* fertilization, higher BPA concentrations were associated with poorer oocyte quality, decreased estradiol levels, and decreased implantation success (Bloom et al., 2011; Ehrlich et al., 2012; Fujimoto et al., 2011; Mok-Lin et al., 2010).

1.1.4 Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L):
BPA was assigned a score of High [H} for developmental toxicity based on: known concern for developmental toxicity for BPA.

Authoritative and Screening Lists:

- BPA is shown to have clear evidence of adverse developmental effects by NTP-OHAaT. This translates to a High score for developmental toxicity.

HIGH: The NTP-CERHR (2008) Expert Panel concluded that there is suggestive evidence that BPA causes neural and behavioral alterations related to disruptions in normal sex differences in rats and mice (0.01-0.2 mg/kg bw-day). The FAO/WHO Expert Panel concluded that while there was broad agreement in a NOAEL of 50 mg/kg bw-day for developmental toxicity, low-level (<1 mg/kg bw-day) effects were uncertain. These conclusions support a hazard designation of High concern, with lower confidence.

Based on review of the ECJRC Addenda of 2008 (publication date 2010), no evidence that BPA is a developmental toxicant was observed in standard development studies in rats and mice. In rats, a maternal LOAEL and fetal NOAEL of 160 and 640 mg/kg/day respectively, were identified. In mice, maternal and fetal NOAELs were 250 and 1000 mg/kg/day, respectively. In a rat multigeneration study, a statistically significant decrease in mean pup body weight gain, with concomitant delays in the acquisition of developmental landmarks (vaginal patency and preputial separation) was observed at 500 mg/kg on post-natal days 7-21 in males and females of all generations (F1-F3). These decreases in pup body weight gain and delays in development were seen in the presence of maternal toxicity. No maternal toxicity and no treatment-related effects were reported in the offspring of animals exposed to 50 mg/kg (ECJRC, 2010).

A two-generation study in the mouse involving exposure to low (µg/kg bw/day range) and high (mg/kg bw/day range) doses of BPA was conducted (Tyl *et al.* 2007). To conclude, BPA caused effects on pregnancy and the offspring (observed as a slightly increased duration of gestation, reduced pup bodyweight during lactation, a slight increase in the incidence of undescended testes at weaning, seminiferous tubule hypoplasia in offspring at weaning, and delayed acquisition of preputial separation), occurring only at the highest dietary concentration 3500 ppm (intake approximately 600 mg/kg/day), an exposure level that also caused mild parental toxicity. Fertility was not affected by BPA exposure. There was no evidence of an adverse effect on the development of the male reproductive tract at low doses of BPA. Overall, the study NOAEL for both general and reproductive toxicity is 50 mg/kg/day (ECJRC, 2010).

The 2-generation study in mice (Tyl *et al*. 2007) provides a comprehensive, definitive, investigation of the effects of BPA on reproduction at exposure levels spanning the low (µg/kg bw/day) to high (mg/kg bw/day) ranges. This study has shown that BPA causes adverse effects on pregnancy and offspring, observed as a slightly increased duration of gestation, reduced pup bodyweight during lactation, a slight increase in the incidence of undescended testes at weaning, seminiferous tubule hypoplasia in offspring at weaning, and delayed acquisition of preputial separation, at 600 mg/kg/day, an exposure level that also caused mild parental toxicity. Fertility was not affected by BPA exposure, which resolves the previous uncertainty regarding the NOAEL for fertility in mice. A study NOAEL for reproductive toxicity of 50 mg/kg/day has been identified. As there was no evidence of an adverse effect on the development of the male reproductive tract at µg/kg bw/day doses of BPA, the study resolves the uncertainties surrounding the potential to produce adverse effects on development at low doses. Thus, the study establishes a NOAEL of 50 mg/kg/day for reproductive toxicity (ECJRC, 2010).

Additionally, some studies have investigated the potential of BPA to affect male reproductive tract development in rats and mice. Conflicting results have been reported in these studies, in both species. In mice, adverse effects on male reproductive tract development (an increase in prostate weight in two studies and a reduction in epididymis weight in one study) have been reported at dose levels in the range 2 – 50 µg/kg. However, these results have not been reproducible in two other studies, one of which included additional dose levels, and using larger group sizes compared with those used in either of the two studies showing effects (ECJRC, 2010).

Based on the data presented in NTP studies, a developmental no observed adverse effect level (NOAEL) of 1280 mg/kg/day (highest dose tested) was identified for CD® rats administered BPA on gestation days (GD) 6-15; a

developmental NOAEL of 1000 mg/kg/day and a developmental lowest observed adverse effect level (LOAEL) of 1250 mg/kg/day was identified for CD-1 mice administered BPA on GD days 6-15. Maternal LOAELs were lower than the developmental NOAELs (160 mg/kg/day in rats and 500 mg/kg/day in mice) in these studies. Two other studies were reviewed; however, their protocols are limited with regard to endpoints beyond fertility (FDA, 2008a).

In the aforementioned studies listed under *Reproductive Toxicity*, a NOAEL for offspring was determined to be 50 mg/kg bw/day in both species and sexes. Although these studies were not considered full teratology studies as described in Redbook 2000 developmental protocols, the comprehensiveness of these studies, including the use of multiple generations, is relevant to the analysis of developmental endpoints. The protocol of continuous exposure is more consistent with human exposure scenarios for BPA. The NTP draft Brief indicated some concern for the current level of exposure to BPA and developmental toxicity to the prostate, urinary tract and early onset of puberty in females. Some of these developmental endpoints were addressed in the multigenerational studies performed by RTI (Tyl 2002 and 2008), though by different methodologies (FDA, 2008a).

In most of the studies reviewed, limitations were cited that decreases confidence in their usefulness in a safety assessment. Some studies had only small numbers of replicates, some used only 1 or 2 doses of BPA so a dose-response relationship could not be determined, some used a non-oral route of administration, which would have affected blood levels and embryonic exposures, and several lacked experimental details that would allow complete analysis of the reported results or independent conclusions based on an evaluation of the raw data. One of the most common weaknesses among these studies is a lack of a measure of internal dose, which is important for comparing the reported findings in published studies which used different routes of exposure. Because even the highly relevant regulatory guideline studies which administered BPA in the diet (the most relevant exposure route) did not measure internal dose, it is not possible to compare the published studies using various routes of exposures and study protocols to the relevant guideline studies with regard to dose of BPA administered and reported findings. Data currently available suggests that studies based on other routes of exposure, such as intraperitoneal or s.c. injections, may not be comparable to possible human exposures through food contact materials, and will not produce realistic safety assessments for this route of exposure (oral) (FDA, 2008a).

FDA considers that BPA exposure to a mother will be continuous, occurring throughout her entire life. Exposure to any offspring will therefore occur throughout gestation, during infancy (whether through breast milk, PC bottles, or infant formula) and on through later development and adulthood. In the presence of continuous exposure, changes or adaptations may occur that impact the potential toxicity of the substance. Accordingly, as is the case for BPA, FDA considers a more accurate assessment of a food additive's potential developmental neurotoxicity to be more relatable to human exposure when examined with exposure occurring throughout the period of development. In addition, since select critical periods may occur at various times during development, the variety of exposure regimens used may have contributed to some of the inconsistent or conflicting findings reported in studies on developmental toxicity potential of BPA (FDA, 2008a).

Acceleration of puberty in female rodents (FDA, 2008a):
Three studies were judged to be useful in performing a safety assessment for BPA exposure through the use of food contact materials; these are the multigeneration studies by Tyl *et al.* (2002, 2008, both reviewed above) and Ema *et al.* (2001). All three studies were conducted under GLP conditions and examined only the day of vaginal opening as the endpoint for determination of the onset of puberty in the female. Tyl *et al.* (2008) used mice; the other studies used rats. The study by Ema *et al.* (2001) reported no effects on the day of vaginal opening at oral doses up to 200 µg/kg bw/day. Although the authors did not identify a NOAEL, it appears that 200 µg/kg bw/day would be a NOAEL for the timing of female puberty; this was the maximum dose used in this study. The study by Tyl *et al.* (2002) reported a delay in vaginal opening at 7500 ppm; this appeared to be due to a decrease in body weight. The study by Tyl *et al.* (2008) used CD-1 mice and reported no effect on the day of vaginal opening at any dose, including the maximum dose of 3500 ppm; however, as indicated in Table 9 of the published study, absolute day of acquisition was not statistically significant at 3500 ppm. Day of acquisition was statistically significantly accelerated when adjusted by body weight on PND 21 for F1 (only animals measured). Again, no findings were reported at the lower doses. Due to the very thorough nature of these studies, FDA has a high level of confidence in their results.

Two mouse studies (Ryan and Vandenbergh, 2006 and Honma *et al.*, 2002) reportedly observed acceleration of the day of first estrus; however, it is noteworthy that the Honma *et al.* study used s.c. exposure and the reported effects were of questionable significance (~1 day). An additional study, Howdeshell *et al.*, 1999, reported a reduction in the

number of days between vaginal opening and first estrus; however, neither the age of vaginal opening nor the age at first estrus were accelerated. Accordingly, this study did not report a potential acceleration in puberty.

Only Honma *et al.* (2002) evaluated the fertility of the animals demonstrating a slight acceleration in first estrus and found no effect on fertility. Although the multigeneration study by Tyl *et al.* (2008) did not evaluate the time of first estrus, they observed no adverse effects on fertility. Ashby *et al.* (1999) also did not observe a change in vaginal opening following treatment of CF-1 mice on GD 11–17 with 0, 2 or 20 µg BPA/kg bw/day76. Taken together, these results suggest that within the context of laboratory animal studies, limited evidence exists regarding an acceleration of puberty and none of the studies indicate an adverse effect on the ability of the mice to reproduce. The relationship of the increment of the responses observed in these studies to human effects, as well as other possible adverse effects which may be associated with accelerated puberty in humans have not been correlated using rodent study data or examined in rodent studies, respectively, for BPA. In fact, the onset or progression of puberty would be an adverse outcome; however, the increment of change in puberty timing considered biologically meaningful was not agreed on for either humans or an animal model as a result of available studies.

Only a very small number of studies evaluated blood levels of BPA and/or its metabolites. The lack of this information complicates the interpretation of conflicting study findings and is demonstrated in the inability to compare the findings with regard to the age of vaginal opening in the studies of Honma *et al*. (2002) and Ashby *et al*. (1999) in which the same doses of BPA were administered during the same gestation period. Honma *et al*. (2002) observed an acceleration of vaginal opening at 20 µg/kg bw/day whereas Ashby *et al*. (1999) observed no effect at the same dose; Honma *et al*. (2002) used the s.c. route while Ashby *et al*. used the oral route. There were other differences in experimental design that may have contributed to the different observations (differences in mouse strains used, in environmental exposure, and in numbers of animals examined), but the different routes of administration cannot be eliminated as a major contributor to the differing results.

Study: Tyl *et al.,* 2008
Dose: 0.018, 0.18, 1.8, 30, 300, 3500 ppm
Exposure Route: In chow
Dose Effect: No change in onset of puberty.

Study: Tyl *et al*., 2002
Dose: 7500 ppm
Exposure Route: In chow
Dose Effect: Statistically significant delay in the onset of puberty.

Study: Ema *et al.,* 2001
Dose: 0.2, 2, 20, and 200 ug/kg bw/day
Exposure Route: Gavage
Dose Effect: No change in onset of puberty

Altered prostate and urinary tract development in males (FDA, 2008a)*:*
Guideline GLP studies using oral exposure (Tyl *et al*., 2002; Tyl *et al*., 2008) throughout the life span, including gestation and weaning, show no evidence of selective reproductive toxicity or effects on male development or prostate at doses at or below 750 ppm (approximate intake of 50 mg/kg bw/day) in the rat or 300 ppm (approximate intake of 50 mg/kg bw/day) in the mouse. Although there were no effects on the prostate at this dose, there was evidence of adverse effects on other male reproductive tissue endpoints, including decreased testis weight and delays in preputial separation and testicular descent. As discussed in *Reproductive Toxicity*, the NOAEL for reproductive and offspring toxicity was 50 mg/kg bw/day. A third such study (rat two generation reproductive study with Sprague-Dawley rats, Ema, *et al*., 2001), likewise found no effect on prostate weight or histology at doses up to 200 µg/kg bw/day. These studies clearly contain datasets that are most useful in a safety assessment because of their size, comprehensive endpoint evaluation, rigorous attention to the certification of doses, and control of experimental conditions (FDA, 2008a).

The study of Tyl *et al.* (2008) is particularly important because it utilizes a strain of mouse that has been reported by others to be sensitive to BPA under different treatment conditions. These studies indicate that perinatal BPA exposure does not adversely affect prostate weight or histology at doses of 0.2 – 50 mg/kg bw/day. Functional

endpoints, such as those examined in some of the smaller studies, might uncover more subtle effects of BPA exposure and would need to be assessed for their long term consequences and relevance to human toxicity prior to utilization in a safety assessment (FDA, 2008a).

There are conflicting results on the effects of BPA on the mouse prostate after oral dosing of dams during gestation only. Some studies report effects at doses between 2 and 50 μg/kg bw/day, while others show no effects at these doses using reportedly similar conditions, or even at much higher doses. Several of the available prostate studies focus on the sensitization to later hormonal stimulation rather than overt toxicity to the prostate, with only subtle treatment-related changes in control of gene expression evident prior to hormonal challenge (FDA, 2008a).

Many of the studies reviewed appear to suggest that developmental BPA treatment can cause alterations in brain development and behavior; however, the limitations noted for individual studies ranged from mild to severe. The majority of the studies appear focused on mechanism testing, rather than safety assessment, and many of the study authors did not clearly define the criteria used in the analysis and had a tendency to inappropriately anthropomorphize behaviors or make exaggerated conclusions regarding the relevance of the results shown. Additionally, many of the studies employed various exposure periods, conditions that would not be expected to occur in human exposure scenarios. The endpoints examined in these studies (behavioral changes related to stress, pharmacological challenges and sexual dimorphism) represent an emerging area in developmental neurotoxicity for which validated protocols are currently unavailable. Major limitations of many of the studies reviewed in this area included a lack of concurrent examination of endpoints used for validating findings (histomorphologic evaluations, hormonal analyses, or neurochemical assessments with which to correlate the treatment-related behavioral effects of perinatal BPA exposure and vice versa) or examining only one sex. In rats dosed orally during development, effects were reported at doses as low as 2.4 μg/kg bw/day (Akingbemi et al 2004; dosed from PND 21 – 35, decreased serum testosterone and luteinizing hormone at PND 35 (no effect at higher doses) and decreased estradiol at 2.4 and 1E+05 μg/kg bw/day (no effect at 2E+05 μg/kg bw/day)). These data suggest findings at relevant doses; however, species/strain differences appear to exist, the dosing regimen utilized is not indicative of the human exposure scenario, and the reporting limitations (lack of experimental details or raw data allowing for critical or independent analysis) of the studies inhibit their use in regulatory decision making. Studies demonstrating BPA-related changes at the molecular level with regard to receptor distribution are interesting from an investigational point of view, but do not readily lend themselves to regulatory decision making. These data collectively suggest that more research, using validated studies with feeding protocols modeling human exposure are necessary prior to establishing a NOAEL for this endpoint for use in regulatory safety assessments (FDA, 2008).

Study: Tyl *et al.,* 2002
Dose: 0, 0.015, 0.3, 4.5, 75, 750, 7500 ppm (approx. 0, 20, 300, 5E03, 5E04, and 5E05 ug/kg bw/day)
Exposure Route: Mixed in diet
Dose Effect: Significant decrease in absolute prostate weight at 7500 ppm (500 mg/kg bw/day)

Study: Tyl *et al.,* 2008
Dose: 0, 0.018, 0.18, 1.8, 30, 300, 3500 ppm (approx. 0, 30, 300, 5E03, 5E04, and 5E05 ug/kg bw/day)
Exposure Route: Mixed in diet
Dose Effect: No effects on prostate weight. Decrease in testis weight, delayed preputial separation and testicular descent at 3500 pm (500 mg/kg/day).

The reliability of several studies (Negishi 2004, Carr 2003, Ryan and Vandenberg 2006 and Adriani 2003) is judged to be adequate by a number of European Union nations based on behavioral testing that: 1) has been conducted according to acceptable methods, 2) the group sizes are quite close or equal to those recommended in the OECD TG 426, and 3) the litter has been used as the statistical unit. The effects found in these studies indicate that there is a possible risk for developmental neurotoxicity of BPA at very low exposure levels (0.1-0.25 mg/kg/d). These effects cannot be dismissed based on the other unreliable studies in the DNT database (ECJRC, 2010).

A 2009 study reported that prenatal exposure was associated with an increase in hyperactivity and aggression in two-year-old girls (Braun et al., 2009). In a follow-up assessment of this cohort of children, average maternal BPA levels were associated with an increase in anxiety and hyperactivity, and poorer emotional control and inhibition in three-year-old girls (Braun et al., 2011b). These results suggest that the behavior of BPA-exposed girls was masculinized. This is perhaps most revealing when considered in the context of animal studies, which have indicated

that BPA can masculinize behaviors of female rodents, and may feminize the behaviors of male rodents (Adewale et al., 2011; Patisaul et al., 2006; Patisaul et al., 2009; Rubin et al., 2006).

Other studies link maternal BPA exposures to an increase in premature births, as well as small for gestational age babies (Cantonwine et al., 2010; Chou et al., 2011; Miao et al., 2011b). Maternal or paternal exposure to BPA during pregnancy was also associated with decreased anogenital distance in sons (Miao et al., 2011a), suggesting feminization of male offspring. Maternal BPA levels also influenced newborn hormone levels that are associated with lipid metabolism (Chou et al., 2011). These results are consistent with a study in mice documenting disruption of glucose homeostasis in mothers and male offspring as a function of increased BPA exposure (Alonso3 Magdalena et al., 2010b). Offspring may therefore be at risk for diabetes or obesity later in life.

Finally, BPA exposure may also influence the developing immune system. Early prenatal exposure, but not later prenatal exposure or neonatal exposure, was associated with an increase in child wheeze at six months of age (Spanier et al., 2012). Additionally, BPA levels were associated with antibody titers to a common pathogen (cytomegalovirus), although the relationship was reversed for individuals younger vs. older than 18 years old (Clayton et al., 2011).

1.1.5 Endocrine Activity (E) Score (H, M or L):

BPA was assigned a score of High [H] for endocrine activity based on: BPA listed as Category 1 substance on the European Union Priority List of suspected endocrine disruptors (Peterson et al., 2007) and based on professional judgment.

Authoritative and Screening Lists:

- BPA is listed as a category 1 substance on European Union Priority List of suspected endocrine disruptors (Peterson et al., 2007) (EU ED). This translates to a Moderate or High concern for endocrine activity.

- BPA is classified as a substance of possible concern by EC/Oslo-Paris Conv - Priority PBTs and EDs & equivalent concern (OSPAR) as a substance of possible concern. This translates to a Moderate or High concern for endocrine activity.

- BPA is listed for toxicity including endocrine disruption by ChemSec Substitute List (SIN). This translates to a Moderate or High concern for endocrine activity.

- BPA is classified as a potential endocrine disruptor in three or more studies by TEDX. This translates to a Moderate or High concern for endocrine activity.

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HIGH: Bisphenol A displays endocrine activity in *in vitro* assays, but yields mixed results in *in vivo* studies. *In vitro* assays demonstrate that bisphenol A can bind to estrogen receptors, elicit estrogen-induced gene transcription, induce progesterone receptors, and induce cell proliferation in MCF7 cancer cells. The data located indicate that the *in vitro* endocrine activity of bisphenol A is approximately 3-5 orders of magnitude less than that of 17β-estradiol, although the results are influenced by cell-type. *In vitro* assays suggest that, bisphenol A did not elicit an androgenic but there is some evidence of anti-androgenic activity. Limited comparative *in vitro* data suggest that the estrogenicity of bisphenol A is similar in magnitude to that of bisphenol AP, bisphenol C, and bisphenol F and somewhat more potent than bisphenol S. Based on *in vitro* data there is also evidence of biological interactions involving rapid signaling networks. Data from in vivo studies exhibit a more complex picture; oral bisphenol A does not consistently produce robust estrogenic responses. EINECS provides summary data to suggest that bisphenol A has been shown to act as an estrogen or xenoestrogen in ecological systems.

Most studies of the health effects of BPA have focused on estrogenic activity because it is widely documented to function as an agonist of certain estrogen receptors (ERs) (Lee et al. 2003) and as an androgen antagonist and to suppress aromatase activity (Bonefeld-Jorgensen et al. 2007) (Melzer et al. 2011). Thyroid hormone disruption (Moriyama et al. 2002), altered pancreatic β-cell function (Ropero et al. 2008), and obesity-promoting effects (Newbold et al. 2008), have also been reported in research studies. Many of these effects are already detectable at intakes less than the current tolerable daily intake (TDI) of 0.05 mg/kg/day prompting concerns that the TDI should be revised (Melzer et al. 2011). However, there has not been a strong body of evidence that BPA at these low levels exerts significant and substantive biological effects in humans until recently. Melzer et al. 2011 found that BPA exposure is associated with *in vivo* estrogenic gene expression in adults and is associated with male infertility. Further, Rissman et al. (2012) found that low dose gestational exposure to BPA, a dose within the reported human levels, leads to trans-generational behavioral changes in mice including increased anxiety, aggression and cognitive impairments for four generations (The Endocrine Society News Room 2012). The study by Rissman et al., *Gestational exposure to Bisphenol A produces trans-generational changes in behaviors and gene expression,* will appear in the August 2012 issue of *Endocrinology* (The Endocrine Society News Room 2012).

It is well-documented that BPA binds to estrogen receptors (ERα and ERβ), although its affinity is orders of magnitude lower than that of endogenous estrogen (Kuiper, 1998). In addition, several *in vitro* studies have indicated that BPA may also interact with other receptors, including membrane bound ER and estrogen-related receptor γ (ERR γ)[6]. Since the late 1990s, a large volume of research has been generated suggesting a possible 'low'

[6] Summarized data cited in CERHR final report NTP-CERHR Expert Panel Report on the

dose effect for weakly estrogenic environmental contaminants, such as BPA. The NTP defines 'low' dose for BPA as ≤ 5 mg/kg bw/day (Melnick, 2002).

A complicating aspect of evaluating the potential adverse effects of endocrine active compounds, especially at low doses, are dietary confounders, i.e. the potential presence of high levels of estrogenically active phytoestrogens and lignans in laboratory, adult and formula-fed infant diets (FDA, 2008a). As BPA has been discussed as binding and acting through ERs (α and β), it is important to consider that *in vivo* BPA is therefore competing for binding to ERs with endogenous estrogen (17β-estradiol, E2) and with much higher levels of these dietary compounds. In fact, BPA has an approximately 1000 - 10,000-fold lower affinity for ERα and ERβ as compared to E29, whereas genistein, a phytoestrogen, has a much higher affinity than BPA for ERα and ERβ10. Accordingly, if equal concentrations were available, the assumed order of binding to the ERs would be E2, genistein, and then BPA (FDA, 2008a).

Altered endocrine function in offspring of BPA exposed rodent dams is suggested by reports of decreased testosterone levels in male offspring, altered thyroxin levels in postnatal pups, and conflicting reports of changes in expression of RC3/neurogranin mRNA (a thyroxine responsive gene), retinoid receptor levels and steroid hormone receptor coactivator-1 mRNA (FDA, 2008a).

BPA has been shown to have endocrine modulating activity in a number of *in vitro* and *in vivo* screening assays. The potency of this activity in these assays generally ranged from 3 to 5 orders of magnitude less than that of oestradiol. No significant oestrogenic activity has been observed with BPA glucuronide *in vitro.* The available data also indicate that there is a marked strain difference in the response to BPA in rats. However, there are no data to indicate the underlying reasons for such differences. It should be noted that these studies investigating endocrine modulating activity are essentially screening tests and many of them employ experimental protocols, which have not undergone any international validation. However, the first phase of the validation of the uterotrophic assay in OECD indicates that this model is robust and reproducible across laboratories. Whilst this assay can be used to identify oestrogenic activity and can be an early screening test, its use for risk characterization purposes is still a matter for discussion. In addition, many of the available *in vivo* studies have used parenteral routes of exposure, the relevance of which are uncertain with respect to relevant routes of human exposure (ECJRC, 2010).

Reproductive and Developmental Toxicity of Bisphenol A, dated November 2007 (accessible at http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPAFinalEPVF112607.pdf) and published as Chapin *et al.* (2008) NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A *Birth Defects Research* (Part B) 83:157–395.

1.2 Group II and II* Human Health Effects (Group II and II* Human)[7]

1.2.1 Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L):

BPA was assigned a score of Low [L] for acute mammalian toxicity based on: the acute oral and dermal toxicity hazard of BPA is Low based on experimental data in animals (i.e., based on LD50 values).

Authoritative and Screening Lists:

- BPA is classified by GHS Japan as a GHS Category 5 for acute oral and dermal toxicity. This translates to a Low concern for acute mammalian toxicity.
- BPA is classified by GHS New Zealand as 6.1E (GHS Category 5) for acute oral toxicity (New Zealand EPA, 2011. This translates to a Low concern for acute mammalian toxicity.
- BPA is not listed on other Authoritative and Screening Lists.

LOW: The acute oral and dermal toxicity hazard of BPA is low based on experimental data in animals.

Bisphenol A (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 of 5 mg/kg body weight per day. There are no specific long-term toxicity studies with BPA other than those conducted to examine its carcinogenicity.

In a United States National Toxicology Program study (NTP, 1982), bisphenol A (BPA) was administered via gavage to F344 rats and B6C3F1 mice in 1.5% acacia oil. The median lethal dose (LD50) values were calculated to be 4.1 g/kg body weight (bw) for male rats, 3.3 g/kg bw for female rats, 5.2 g/kg bw for male mice and 4.1 g/kg bw for female mice. The Center for the Evaluation of Risks to Human Reproduction (CERHR) panel on BPA (Chapin et al., 2008) summarized additional data on acute toxicity; the lowest reported oral LD50s for rat, mouse, guinea-pig and rabbit are 3250, 2400, 4000 and 2230 mg/kg bw, respectively. An intraperitoneal study referenced in Chapin et al. (2008) gave an LD50 of 150 mg/kg bw in the mouse.

E-FAST28 modeling of BPA releases in the 2007 TRI showed the most conservative estimates of the potential acute dose rate for ingestion of BPA in drinking water by children ages 1-2 ranged from 0.0000531 to 16.5 µg/kg/day, and the most conservative estimates of the surface water concentration ranged from 0.000574 to 232 µg/L. The E-FAST2 model is intended to be used for screening level exposure characterization. E-FAST2 is based on numerous assumptions that are designed to be conservative; for example, E-FAST2 does not account for the half- life of a chemical in surface water. The inputs selected for the E-FAST2 modeling of BPA were also selected to be conservative; for example, the bioconcentration factor was selected to be at the high end of the range of values reported for BPA in the literature.

No dermal lethal concentration (LDLo) for humans or dermal LD50 (the dose required to produce mortality in 50% of the exposed population) has been identified for BPA. The absence of these data precludes adequate evaluation of the acute dermal toxicity of BPA (CDC, 2011).

No useful information is available on the effects of single exposure to BPA in humans. Oral LD50 values beyond 2,000 mg/kg are indicated in the rat and mouse, and dermal LD50 values above 2,000 mg/kg are evident in the rabbit. Few details exist of the toxic signs observed or of target organs. For inhalation, a 6-hour exposure to 170 mg/m^3 (the highest attainable concentration) produced no deaths in rats; slight and transient slight nasal tract epithelial damage was observed. These data indicate that BPA is of low acute toxicity by all routes of exposure relevant to human health (ECJRC, 2010).

[7] Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

1.2.2 Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

Group II Score (single dose: vH, H, M or L);
BPA was assigned a score of Moderate [M] for systemic toxicity/organ effects-single exposure, based on: EU H-Statement classification of H335 and an EU Risk Phrase of R37 for specific target organs/systemic toxicity following single exposure (irritating to respiratory tract). It is noted that BPA was classified as a Category 1 compound by GHS Japan; however, GHS Japan is considered a Screening List whereas the EU Risk Phrase is an Authoritative List. Therefore, the score is Moderate based on the Authoritative Listing and professional judgment.

Group II* Score (repeated dose: H, M or L):
BPA was assigned a score of Moderate [M] for systemic toxicity/organ effects-repeated exposure, based on: an EU H-statement classification of H335 and GHS Japan classification of Category 2 (respiratory organs, liver, kidneys) for specific target organs/systemic toxicity following repeated exposure and data evaluation.

Authoritative and Screening Lists:

- BPA was classified as H335 by EU H-Statements as BPA may cause respiratory irritation. This translates to Moderate concern for specific target organs/systemic toxicity (respiratory tract).

- BPA was assigned an EU Risk Phrase of R37 for single exposure, irritating to respiratory system. This translates to Moderate concern for specific target organs/systemic toxicity following single exposure.

- BPA is classified by GHS Japan as Category 1 (respiratory organs) and Category 3 (narcotic effects) for specific target organs/systemic toxicity following single exposure. This translates to Very High concern and a Moderate concern, respectively, for specific target organs/systemic toxicity following single exposure.

- BPA is classified by GHS Japan as Category 2 (respiratory organs, liver, kidneys) for specific target organs/systemic toxicity following repeated exposure. This translates to High concern for specific target organs/systemic toxicity following repeated exposure.

USEPA has established a chronic oral reference dose (RfD) of 5E-02 mg/kg-day for use in assessing human health exposures. This value was established in 1988, based primarily on a 1982 NTP study which presented a Low Observable Adverse Effect Level (LOAEL) of 50 mg/kg-day, based on reduced body weight in the rat as the critical effect and incorporating an Uncertainty Factor of 1000 (USEPA, 2012).

In consideration of possible age-dependent toxicokinetics of BPA in animals and humans and their implication for hazard and risk assessment of BPA in food, the European Food Safety Authority Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) Panel concluded that the exposure of a human fetus to free BPA would be negligible due to the maternal capacity for conjugation, whereas the fetal rat would be exposed to free BPA from the maternal circulation. Taking account of data in human neonates on compounds structurally related to BPA which undergo glucuronidation/sulphation, the Panel considers that there is sufficient capacity in the neonate to conjugate BPA at doses below 1 mg/kg bw (the Panel noted that exposures at the TDI of 0.05 mg/kg bw are 20 fold lower than this) (EFSA, 2008a).

The EFSA Panel concluded that there is sufficient capacity for biotransformation of BPA to hormonally inactive conjugates in neonatal humans at exposures to BPA that were considered in the EFSA opinion of 2006 and the European Union Risk Assessment Report (EU, 2003, 2008). In addition, the Panel noted that because of the metabolic differences described, exposure to free BPA in adult, fetal and neonatal rats will be greater than in humans and that rats would therefore be more susceptible to BPA-induced toxic effects than humans on an equivalent dose basis. The Panel therefore considers that its previous risk assessment based on the overall NOAEL for effects in rats and using a default uncertainty factor of 100 can be considered conservative for humans. The Panel concluded that the differences in age-dependent toxicokinetics of BPA in animals and humans would have no implication for the EFSA 2006 risk assessment of BPA (EFSA, 2008a).

The systemic toxicity of BPA has been examined in numerous studies. Studies fully reviewed included a 2-week aerosol toxicity study with Fischer 344 rats, a 90-day oral toxicity study in dogs, and a 13-week aerosol toxicity study with Fischer 344 rats. It is noted that the multi-generation studies discussed under *Reproductive Toxicity* contained a subchronic period preceded by *in utero* exposure. These studies reported NOAELs of 5 mg/kg bw/day for systemic effects (FDA, 2008a).

Although FDA had previously reviewed BPA studies in which the method of exposure was aerosol administration, these were not considered useful in evaluating oral exposure, but were evaluated due to their robustness for the identification of potential target organs (FDA, 2008a).

No epidemiological studies that evaluated the potential of BPA to cause systemic effects were identified. A single study investigating the transfer of BPA to the skin during the handing of thermal printing paper containing BPA was identified [Beidermann et al. 2010]. The findings of the study demonstrate the contamination of the skin with BPA, which was highly variable based on the condition of the skin and exposure scenario. Beidermann et al. [2010] concluded that BPA was transferred to the skin during the handing of the thermal printing paper, but due to the nature of the study, its ability to penetrate the skin and contribute to systemic dose could not be defined (CDC, 2011).

No information was available on potential systemic effects in animals following repeat-dose (21-day or 28-day), subchronic (90-day), or chronic (at least 12-month) dermal exposure to BPA. DuPont [1962] stated that results of experimental studies and actual experience with BPA elicited no systemic effect from occasional contact with the chemical (CDC 2011).

None of the reviewed or cited studies indicate a concern at the current cumulative estimate daily intake (CEDI) (FDA, 2008a). Furthermore, all recent reviews of BPA have focused on the pivotal endpoints of reproductive and developmental toxicity.

Study: 2-week/rat/inhalation/Dow Chemical U.S.A. (1985)
- **BPA Dose:** 0, 10, 50 or 150 mg/m3
- **Dose Effects:** 150 mg/m3: Decreased body weight gain (males), decreased abdominal fat
  50, 150 mg/m3: Anterior nasal inflammation and/or epithelial hyperplasia (both sexes)
- **NOAEL/Comments:** 10 mg/m3 (low confidence due to deficiencies noted in review)

Study: 90-day/dog/diet/International Research and Development Corporation (1976)
- **BPA Dose:** 0, 1000, 3000, 9000 ppm
- **Dose Effect:** 9000 ppm: increased liver weights
- **NOAEL/Comments:** 3000 ppm* (low confidence due to deficiencies noted in review)

Study: 13-week/rat/inhalation/Dow Chemical Co. (1988)
- **BPA Dose:** 0, 10, 50 or 150 mg/m3
- **Dose Effects:** ≥ 10 mg/m3: Decreased body weight
  50, 150 mg/m3: enlarged cecum, hemolyzed blood present in stomach, perineal and facial soiling, very slight goblet cell hyperplasia in the respiratory epithelium and nasal turbinates.
- **NOAEL/Comments:** No NOAEL available; LOAEL of 10 mg/m3 (low confidence due to deficiencies noted in review)

Study: 90 day/F344 rat/dietary/NTP (1982)
- **BPA Dose:** 0, 250, 500, 1000, 2000, 4000 ppm
- **Dose Effects:** ≥ 1000 ppm (100 mg/kg bw/d): decreased body weight gain
  250 ppm: hyaline masses in bladder lumen (males)
  All (except 250 ppm females): caecal enlargement
- **NOAEL/Comments:** NOAEL of 250 ppm (25 mg/kg bw/d) in females; LOAEL of 250 ppm (25 mg/kg/d) in males

Study: 90 day/B6C3F1 mice/diet/NTP (1982)

BPA Dose:	0, 5000, 10000, 15000, 20000, or 25000 ppm
Dose Effects:	≥ 15000 ppm (1950 mg/kg bw/d): reduced body weight gain (males) ≥ 5000 ppm (650 mg/kg bw/d): reduced body weight gain (females) ≥ 500 ppm (600 mg/kg bw/d) multinucleated giant hepatocytes with dose related increase in incidence and severity (males)
NOAEL/Comments:	No NOAEL available. LOAEL: 5000 ppm (600 mg/kg bw/d in males)

1.2.3 Neurotoxicity (N) Score (vH, H, M, or L):

Group II Score (Single Dose vH, H, M or L):
BPA was assigned a score of DG [default, H] for neurotoxicity-single exposure, based on: lack of relevant data.

Group II* Score (Repeated Dose H, M or L):
BPA was assigned a score of DG [default, H] for neurotoxicity-repeated exposure, based on: lack of relevant data.

Authoritative and Screening Lists:

- BPA was not found on relevant authoritative or screening lists.

DATA GAP: Confidence in the reliability of the developmental neurotoxicity database is low because of limitations in the design and reporting in all of the available studies. These limitations include small group size, inappropriate statistical analysis, brief reporting of methods and results, lack of compliance with GLP and use of one BPA dose level. The receptor/neurotransmitter level studies are regarded as mode of action or mechanistic investigations and cannot be used as the primary support for conclusion regarding the hazardous properties of BPA. The consistency assessment shows that there is no discernible and reproducible pattern to the behavioral testing results. Most of the studies investigating effects at the receptor/neurotransmitter level and brain morphology have not been replicated by independent laboratories, so consistency cannot be assessed. Overall, taking together the low confidence in the reliability of the developmental neurotoxicity studies and the lack of consistency in the results of behavioural testing, no conclusions can be drawn from the preeminent studies (Negishi 2004, Carr 2003, Ryan and Vandenberg 2006 and Adriani 2003). This opinion is very similar to that of EFSA (2006), who reviewed nine of the developmental neurotoxicity studies. There is dissention among participating European Union nations as to the reliability of these studies. The reliability of Negishi 2004, Carr 2003, Ryan and Vandenberg 2006 and Adriani 2003, is alternately judged to be adequate by a number of European Union nations based on behavioral testing that: 1) has been conducted according to acceptable methods, 2) the group sizes are quite close or equal to those recommended in the OECD TG 426, and 3) the litter has been used as the statistical unit. The effects found in these studies indicate that there is a possible risk for developmental neurotoxicity of BPA at very low exposure levels (0.1-0.25 mg/kg/d). These effects cannot be dismissed based on the other unreliable studies in the DNT database (ECJRC, 2010).

1.2.4 Skin Sensitization (SnS) Group II* Score (H, M or L):

BPA was assigned a score of Moderate [M] for skin sensitization based on: positive results in skin sensitization tests on BPA and data evaluation results.

Authoritative and Screening Lists:

- BPA carries an EU Risk Phrase of R 43 as BPA may cause skin sensitization by skin contact. This translates to a High or Moderate score for skin sensitization.

- BPA is classified as Category 1 by GHS Japan based on a positive test for skin sensitization. This translates to a High or Moderate score for skin sensitization.

MODERATE: Recent data from three BPA manufacturing facilities indicate that BPA does not elicit skin sensitization. However, results of some human studies suggest the possibility of a dermal sensitization response, although cross-sensitization was not ruled out. Most animal studies were negative for dermal sensitization, although assays may not have been maximized. There is evidence of ear swelling in a photoallergy test in mice and moderate redness and swelling following repeated dermal exposure in rabbits. Based on suggestive evidence of skin sensitization in humans and mice, a MODERATE hazard designation is warranted.

The skin sensitization potential of BPA has been evaluated in several case reports and predictive animal studies (mouse ear-swelling test). The weight of evidence indicates that BPA is a skin sensitizer and can cause photoallergy (CDC, 2011). The equivalent dermal designation for BPA, according to the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, is Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) (CDC, 2011).

No studies of BPA in humans or experimental animals following dermal exposure were identified. Morck et al. [2010] conducted a series of *in vitro* experiments to evaluate the potential adverse effects of BPA exposure during pregnancy. As part of this study, dermal absorption was examined using an *in vitro* diffusion model that employs full thickness human skin. The authors reported that the skin was exposed to 17.5 millimolar BPA for 48 hours in the donor chamber and samples were collected from the receiving chamber at regular time intervals. Among the reported results, 13% of the applied BPA was recovered within 48 hours in the receiving chamber, which represents dermal absorption. Approximately, 7.4% and 17% of the applied dose of BPA were recovered within the epidermis and dermis, respectively. Morck et al. [2010] concluded that more than 1/3 of the applied dose of BPA was dermally absorbed and may be available systemically. Kaddar et al. [2008] investigated the potential for BPA to be percutaneously absorbed through an *in vitro* diffusion model using pig skin. A solution of radiolabelled BPA, 10 micrograms per milliliter (μg/mL) in physiological serum, was placed on skin samples mounted within modified Franz static diffusion cells. Kaddar et al. [2008] reported that after 2, 5, and 10 hours of exposure, the total BPA skin content was 3%, 6.9%, and 11.4% of the applied dose. After 10 hours, 64.8% of the applied dose remained on the surface of the skin, 5.4 % of the applied dose was located within the epidermis, and 8.8% of the applied dose was contained within the dermis. Kaddar et al. [2008] concluded that BPA remained primarily on the skin surface and the chemical accumulated primarily in the dermis (CDC, 2011).

Medical surveillance information obtained from 5 out of the 6 BPA manufacture plants present in the EU was recently provided by industry (PlasticsEurope, 2007). During BPA manufacture, workers may be exposed to phenol, acetone and BPA. As phenol and acetone are not skin sensitizers, the assessment of the potential skin sensitizing activity of BPA is not confounded by exposure to other chemicals in these factories. In company A, no cases of skin sensitization were identified among 110 workers examined since 1991 (site 1) and among 190 workers examined since 1984 (site 2). In company B, no cases of dermatitis were identified among 500 workers examined since 1976, and in company C, no cases were identified among 75 workers (ECJRC, 2010).

A recent LLNA study has shown that BPA does not possess skin sensitization potential. However, in this study, the concentration of BPA was not maximized. Therefore, there remains some uncertainty as to whether high concentrations (> 30%) of BPA can still exert skin sensitizing activity. Similarly, a recent photo-LLNA has shown that BPA does not possess skin photo-sensitization potential. However, again, in this study, the concentration of

BPA employed was not maximized. Although there are sporadic reports showing that BPA in the presence of UV light can elicit skin responses in humans, comprehensive medical surveillance data obtained from BPA manufacture plants has shown that no cases of skin sensitization have been identified among approximately 875 employees examined for several years. Due to the nature of these data, although it can be concluded that the risk of skin sensitization is low under the exposure conditions experienced by these workers, a potential skin sensitization hazard cannot be completely excluded. Overall the new information does not confirm the previously reported evidence of a skin sensitization potential of BPA. While the data do not exclude a skin sensitizing activity of BPA at high concentrations (> 30%), there is no evidence that this is a concern for workers in current BPA manufacturing plants (such workers are believed to represent the group most likely to be exposed to BPA dust) (ECJRC, 2010).

1.2.5 Respiratory Sensitization (SnR) Group II* Score (H, M or L):

BPA was assigned a score of Low [L] for respiratory sensitization, based on: data evaluation.

Authoritative and Screening Lists:

- Not classified on GHS Japan list.

- BPA was not found to result in respiratory sensitization on relevant authoritative or screening lists.

In a two-week inhalation study, rats were exposed to 10, 50 or 150 mg/m^3 of BPA aerosol for 6 hr/day for nine exposures. A decrease (about 5%) in body weight gains of male rats exposed to 150 mg/m^3 was observed. Microscopic changes, indicative of slight irritation, were observed in the anterior portion of the nasal cavity of rats exposed to 50 or 150 mg/m^3 (Nitschke et al., 1985).

This study was followed by a 13-week inhalation study (6 hr/day, 5 day/week) where very slight to slight alterations of the upper respiratory tract were observed in rats exposed to 50 or 150 mg/m^3 (Nitschke et al., 1985). The lesions were described as very slight to slight hyperplasia of the stratified squamous epithelium, respiratory epithelium and very slight to slight inflammation of the underlying submucosa. These changes were consistent with an adaptive response following a slight irritation of the upper respiratory tract. Examination of rats allowed to recover for 12 weeks following exposure to 150 mg/m^3 indicated that the changes were fully reversible. Slight stress-related effects (decreased body weight, perineal soiling from urine and porphyrin-like material around the nose and eyes) were observed at all concentrations of BPA, although food consumption was not decreased. Terminal body weight of male rats at all exposure levels were not statistically different from control values, whereas the terminal body weight of females exposed to 140 mg/m^3 was statistically decreased from controls (~11%). Except for decreased body weight of male rats exposed to 150 mg/m^3 (although not statistically significant at ~6% decrease), these stress-related effects disappeared quickly following cessation of exposure. Enlarged ceca were observed in rats necropsied the day after the final exposures to 50 or 150 mg/m^3 but were not present in rats sacrificed 12 weeks later. Enlarged ceca were most likely the result of ingestion of BPA due to grooming and/or clearance from the respiratory tract. The No Observed Effect Level (NOEL) in this study was 10 mg/m^3, based on the slight to very slight histopathological alterations observed in the upper respiratory tract.

Particle size measurements indicated the majority of the solid aerosol particles generated in this study were in the respirable range (range 1.5 to 5.2 microns depending on the method used). Assuming 100% absorption of the inhaled BPA and respiratory minute volume of 0.8 liters/kg/min (Costa and Tepper, 1988), these exposures are calculated to be equivalent to doses of approximately 43, 13 and 3 mg/kg/day for the 150, 50 and 10 mg/m^3 exposure levels respectively. However, due to the effectiveness of the upper respiratory tract in removing dusts, it should be recognized that the dose which was delivered to the target organ (i.e.: the upper respiratory tract) in this study was likely to be significantly greater on a tissue weight basis than the dose calculated to be "systemically" available. Hence the use of systemic dose of 3 mg/kg/day as the NOEL for risk assessment for routes of exposure other than inhalation is inappropriate.

Slight and transient nasal tract epithelial damage was observed in rats exposed to BPA dust at 170 mg/m3 for 6 hours. Slight local inflammatory effects in the upper respiratory tract were observed in rats exposed to 50 mg/m3 and 150 mg/m3 of BPA in 2 and 13 week repeat inhalation studies, but were not observed at 10 mg/m3 in the same studies. Increased duration of exposure did not increase the severity of the response at 50 and 150 mg/m3. Taken together with anecdotal human evidence, these data suggest BPA has a limited respiratory irritation potential (ECJRC, 2010).

1.2.6 Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L):

BPA was assigned a score of Low [L] for skin irritation/corrosivity based on: low concern for irritation from BPA.

Authoritative and Screening Lists:

- BPA was listed as H317 by EU H-Statements as BPA may cause an allergic skin reaction. This translates to Low concern for skin irritation.

- BPA is not classified by GHS Japan as a skin irritant. This translates to Low concern for skin irritation.

LOW: No data on the corrosivity of BPA from *in vitro* tests with human or animal skin models or on skin integrity from *in vitro* tests with cadaver skin were identified. However, a limited number of skin irritation studies involving animals have been conducted. Shumskaya [1961] evaluated the local effect of BPA on the skin by applying an unspecified amount of pure BPA powder or 10% ointment in Vaseline to shaved areas (4 × 4 cm) of skin on the backs of rabbits. One application of the pure powder did not produce a pronounced skin reaction. However, repeated dermal applications (30 times in 37 days) of the powder caused moderate swelling and redness, which began after the 7th application and lasted for 12 days. After Day 15, the skin turned yellow, followed by dark pigmentation. The investigator reported that the skin of rabbits became dry and began to desquamate and pigment one week after repeated application of the 10% ointment in Vaseline. Shumskaya [1961] concluded, however, that BPA had an insignificant local irritating effect on the skin. DuPont [1962] observed only a very slight, simple irritation on the skin of rabbits following continuous contact with the dry powder under a bandage, over a two-week period. In this study, three similar applications of dry powder to abraded skin produced practically no irritation, whereas application of a 10% aqueous solution under occlusion was slightly irritating to the rabbits. Thorgeirsson and Fregert [1977] observed no irritation to guinea pig skin following a 24-hour occlusive exposure in acetone. In a more recent study, Vohr et al. [2004] found no irritating potential for BPA when they exposed mice to BPA up to its solubility limit (reported as 30%); the investigators used a modified local lymph node assay (LLNA) and the Integrated Model for the Differentiation of Skin reactions (IMDS). No predictions from the structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, were available for BPA. Hulzebos and Gerner [2010] evaluated the potential of BPA to act as a skin irritant using the Integrated Assessment Scheme (IAS). This evaluation tool is designed to critically assess multiple lines of toxicological data to determine the potential of a substance to cause skin irritation. Hulzebos and Gerner [2010] predicted that BPA is not a skin corrosive or irritant based on the results of the IAS analysis (CDC, 2011).

Limited human anecdotal information of uncertain reliability is available from written industry correspondence suggesting that workers handling BPA have in the past experienced skin, eye and respiratory tract irritation. It cannot be determined whether the reported skin reactions were related to skin sensitization or irritation. However, a recent well-conducted animal study clearly shows that BPA is not a skin irritant (ECJRC, 2010). Taken together, the results of the reviewed study indicate that BPA has limited or no potential of causing direct effects of the skin, including corrosion or irritation.

1.2.7 Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L):

BPA was assigned a score of Very High for eye irritation/corrosivity based on: known eye irritation.

Authoritative and Screening Lists:

- BPA was listed as H318 EU H-Statements as BPA causes serious eye damage. This translates to a Very High for eye irritation.

- BPA carries an EU Risk Phrase of R41 due to risk of damage to eyes. This translates to a Very High score for eye irritation.

- BPA is classified as Category 1 by GHS Japan based on a positive test for eye irritation. This translates to a Very High score for eye irritation. GHS Japan notes that while irritating, BPA was not corrosive to the eye.

- BPA is classified as 8.3A by GHS New Zealand due to corrosivity to ocular tissue. This translates to a Very High score for eye irritation/corrosivity.

A recent well conducted animal study shows that BPA is an eye irritant; effects persisted until the end of the study (day 28 postinstillation) in 1 of 3 rabbits. Overall, taking into account the animal and human evidence, BPA has the potential to cause serious damage to the eyes. (ECJRC, 2010).

1.3 Ecotoxicity (Ecotox)

1.3.1 Acute Aquatic Toxicity (AA) Score (vH, H, M or L):

BPA was assigned a score of High [H] for acute aquatic toxicity based on: known to have acute aquatic toxic effects. While screening lists (GHS Japan and GHS New Zealand) indicate potential High concern, an authoritative list (EU Risk Phrase) indicates Moderate concern. Greater confidence exists for authoritative lists; however data gaps are significant, given current indications.

Authoritative and Screening Lists:

- BPA carries an EU Risk Phrase of R52 as BPA is considered harmful to aquatic organisms from acute exposure. This translates to Moderate concern for acute aquatic toxicity.

- BPA is classified as Category 2 by GHS Japan based on 96 hours LC50=1,100 mg/L of crustacean (Mysid Shrimp). This translates to High concern for acute aquatic toxicity.

- BPA is classified as Category 9.1D (GHS Category 2 or 3) by GHS New Zealand for aquatic toxicity. This translates to a Moderate or High concern for acute aquatic toxicity.

HIGH: BPA is considered to be an "organizational disruptor" which can induce long-term detrimental population responses (e.g., changes in sex ratios) if developing organisms are exposed for short periods of time to the compound during a critical developmental window. Hence, under the right conditions, such as in the spring when larval fish or amphibians are developing in BPA-affected water bodies, acute exposures to BPA can have life-long consequences for the affected organisms at concentrations much below those which would cause direct toxicity.

Unlike an "activational disruptor" which causes detrimental changes in an already-formed organ (i.e., the mode of action for many chemical compounds), the effects of BPA need to be assessed at the maximum concentrations likely to be found in impacted bodies of water.

1.3.2 Chronic Aquatic Toxicity (CA) Score (vH, H, M or L):

BPA was assigned a score of Low [L] for chronic aquatic toxicity based on: high potential to rapidly degrade and low bioaccumulation.

Authoritative and Screening Lists:

- BPA is not classified by GHS Japan as having chronic aquatic toxicity due to high potential to rapidly degrade (2-4 days in water) and low bioaccumulation (BCF=67.7). This translates to Low concern for skin irritation.

- It is noted that the PBT Profiler indicates only 8% partitioning to water and a half-life in water of 38 days, suggesting chronic aquatic toxicity not likely.

Several studies with fish have shown that chronic exposures to relatively high but environmentally-relevant levels of BPA (<1.0 – 20 µg/L) in surface water can contribute to growth changes, feminization, alterations in gonadal functions, changes in sperm count, timing in reproduction, or intersex.

For example, Kwak *et al*., 2001 (as reported in Crain *et al*., 2007) calculated a chronic value (i.e., the geometric mean of the NOEC and LOEC) of BPA for tail length changes in the swordtail fish (*Xiphophorus helleri*) equal to 0.63 µg/L.

Exposing male fathead minnows (*Pimephales promelas*) to 16 µg/L or more BPA in surface water resulted in significant changes in testicular function (Sohoni *et al*, 2001, as reported in Crain *et al*., 2007).

Brown trout (*Salmo trutta*) exposed to BPA levels ranging from 1.75 to 5.0 µg/L experienced reduced sperm density and motility, and delayed ovulation, among other responses (Lahnsteiner *et al*, 2005, as reported in Crain *et al*., 2007).

The available body of evidence indicates an apparent absence of reproductive effects of BPA at environmentally relevant concentrations in most groups of invertebrates. Several studies with aquatic invertebrates, however, have shown that BPA can affect the gonadal functions and sexual maturation of these organisms at environmentally relevant concentrations. The results of these studies were contradicted by additional studies which were unable to reproduce the original responses, suggesting that more research is needed in this area.

1.4 Environmental Fate (Fate)

Based on the Level III fugacity models incorporating the located experimental property data, bisphenol A is expected to partition primarily to soil. Bisphenol A is expected to be moderately mobile in soil based on experimental K_{oc} studies. Leaching of bisphenol A through soil to groundwater is not expected to be an important transport mechanism. Estimated volatilization half-lives indicate that it will be nonvolatile from surface water. Volatilization from dry surfaces is also not expected based on its measured vapor pressure. In the atmosphere, bisphenol A is expected to exist in the particulate phase, based on its measured vapor pressure. Particulates will be removed from air by wet or dry deposition.

1.4.1 Persistence (P) Score (vH, H, M, L, or vL):

BPA was assigned a score of Low [L].There is significant disagreement among sources, with directly contradictory findings. To select a hazard level, the hazard score from the media/compartment with the highest percent in the medium is selected.

LOW: Bisphenol A has passed Ready Biodegradability tests, OECD 301 F and OECD 301C within the 10 day window. Experimental data using a wide variety of innocula have demonstrated that rapid primary and ultimate biodegradation of BPA occurs under aerobic condition in water and soil. The biodegradation of BPA does not result in the formation of stable metabolites. Aerobic biodegradation processes are anticipated to be the predominant environmental removal process. Experimental data indicate that BPA does not biodegrade under anaerobic conditions. Although models suggest that BPA may display limited partitioning to sediment, it has been detected in sediment samples. BPA may also undergo removal by both direct and indirect photolysis in environmental waters, although this process is anticipated to be far slower than aerobic biodegradation processes.

BPA is a solid at room temperature. It has a low vapor pressure, moderate water solubility, and low volatility (HSDB, 2009). It has low to moderate mobility in soil. It is expected to biodegrade under environmental conditions, although conflicting results have been obtained using biodegradation screening tests. However, the weight of evidence suggests that it is not expected to be persistent in the environment, and degradation is expected to occur. The rate of atmospheric photooxidation is rapid. Hydrolysis is expected to be negligible under environmental conditions since BPA does not contain functional groups that are susceptible to hydrolysis (ECJRC, 2010).

A short atmospheric half-life of 0.2 days is calculated for the reaction of bisphenol-A with hydroxyl radicals (EU, 2003). The physical and chemical properties of bisphenol-A suggest that hydrolysis and photolysis are likely to be negligible.

From the biodegradation studies reported bisphenol-A would appear to be readily biodegradable, possibly with a short period of adaptation. The default rate constant for biodegradation in wastewater treatment plant is k=1 h-1 for a readily biodegradable substance meeting the 10-day window. This value will be used in the assessment. The resulting fate in a wastewater treatment plant as estimated by European Union System for the Evaluation of Substances (EUSES) is 12% to water and 6.2% to sludge, with 81.9% degraded and a negligible fraction to air (ECJRC, 2010).

A number of studies on the degradation of bisphenol-A in natural waters were also summarized (EU, 2003). Removal appears to be rapid once the waters have become acclimatized to bisphenol-A. The reported lag-phases before degradation are between 3-8 days. After the lag-phase, removal was rapid, with 50% removal in 1-2 days and 100% removal in 2 to 17 days. These data would appear to indicate that in natural waters bisphenol-A may be classed as readily biodegradable, meeting the 10-day test window. The default rate constant for biodegradation of 4.7.10-2 d-1 probably under-estimates the removal rate, as it corresponds to a half -life of 15 days with 97% removal taking 75 days (ECJRC, 2010).

No information was available on the degradation rate of bisphenol-A in soil. Therefore, the degradation rate was estimated from the degradation rate of bisphenol-A in surface water and the soil-water partition coefficient. The half-life for biodegradation of bisphenol-A in soil and the first order rate constant for degradation in soil were calculated by EUSES as 30 days and 0.0231 d-1, respectively, based upon bisphenol-A being readily biodegradable in surface waters (ECJRC, 2010).

Fent *et al.* (2003) studied the adsorption and degradation of bisphenol-A in soils from Germany: three soils from North-Rhine Westphalia and one from Rhineland Palatinate. The adsorption/desorption studies were carried out according to the Organisation for Economic Co-operation and Development (OECD) Guideline 106, the soil degradation studies according to a Society of Environmental Toxicology And Chemistry (SETAC) design. For the degradation study, 12 test systems were set up for each soil type. Bisphenol-A (uniformly labeled with 14C) was applied at 6 µg/100 g soil. Experiments were continued for 120 days. The test systems were analyzed at intervals for the amount of extractable, non-extractable and volatile radioactivity (volatiles captured in soda lime trap for CO2 and oil-wetted quartz wool for VOCs), as well as how much bisphenol-A remained in the system. Bisphenol-A rapidly formed bound residues in soil. After one hour, 19-59% of the applied radioactivity was non-extractable under normal conditions (methanol plus 5% acetic acid). After three days, 84.7 – 88.6% was not extractable. Following hot flux extraction, only a further 2.8% was removed, so that less than 7.4% was extractable using both techniques combined. At the end of the 120 days exposure, less than 2% of the applied radioactivity was extractable. Depending on the soil, 13.1 – 19.3% of the label was recovered as CO2 after the incubation period. No other volatile radioactive species were found. In one soil, after 1-2 hours, 49.2% of the bisphenol-A applied could be recovered, with 33% as other extractable species (up to five different metabolites). After three days, the amount was less than the detection limit (1 µg/kg). No significant metabolites could be found after three days (ECJRC, 2010).

Based on the criteria set forth in EPA's policy statement on *Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances* (64 Fed. Reg. 60194, November 4, 1999), BPA is expected to have low persistence (P1) and low bioaccumulation potential (B1). (EU, 2003, 2008).

Any residual, unreacted BPA remaining in polycarbonate products and epoxy resins can leach out into food or the environment. Polycarbonate is generally stable, but some BPA can be released from polycarbonate when it is exposed to strongly basic conditions, UV light, or high heat. Epoxy resins made with BPA are stable; only residual BPA is expected to be released from epoxy resins.

1.4.2 Bioaccumulation (B) Score (vH, H, M, L, or vL):

BPA was assigned a score of Very Low [vL] for bioaccumulation based on: no evidence of bioaccumulation. The measured bioconcentration factor (BCF) values in fish for bisphenol-A are in the range 30-75, with slightly higher values for other aquatic organisms (tadpoles, clams). These values are well below the threshold of 100. Also, the log K_{ow} is 3.32 (measured), which is below the threshold of log K_{ow}=4 (PHYSPROP, 2012).

LOW: The measured fish BCF values reported for a number of experimental studies are <100.

Based on the criteria set forth in EPA's policy statement on *Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances* (64 Fed. Reg. 60194, November 4, 1999), BPA is expected to have low persistence (P1) and low bioaccumulation potential (B1). (EU, 2003, 2008).

- *Persistence*: Bisphenol-A is readily biodegradable, and so does not meet the P criterion.
- *Bioaccumulation*: The measured BCF values in fish for bisphenol-A are in the range 30-75, with slightly higher values for other aquatic organisms (tadpoles, clams). These values are well below the threshold, and so bisphenol-A does not meet the B criterion.
- *Toxicity*: There are no reliable chronic NOEC values below 0.01 mg/l, although there are some less reliable values and indications of possible effects at this level. Bisphenol-A has been shown to have effects on the endocrine systems of a number of organisms. It is, therefore, considered to meet the T criterion.

Conclusion: Bisphenol-A is not a PBT or vPvB substance; it meets the T criterion but not the P or B criteria.

1.5 Physical Hazards (Physical)

1.5.1 Reactivity (Rx) Score (vH, H, M or L):

BPA was assigned a score of Low [L] based on: BPA scores a 0 according to the HMIS and NFPA ratings for reactivity. Also, GHS "not classified" for reactivity.

Flammability (F) Score (vH, H, M or L):

BPA was assigned a score of Low [L] based on: BPA scores a 0 according to the HMIS and NFPA ratings for flammability. Also, GHS "not classified" for flammability.

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Appendix 1
EPISuite Modeling Results – Bisphenol-A

- **EPISuite Results for Chemical Name (CAS #80-05-7)**
- **ECOSAR Results for Chemical Name (CAS #80-05-7)**

CAS Number: 80-05-7
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29

---------- EPI SUMMARY (v4.10) ----------

Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

KOWWIN Program (v1.68) Results:
==========

Log Kow(version 1.68 estimate): 3.64

Experimental Database Structure Match:
Name : DIPHENYLOLPROPANE
CAS Num : 000080-05-7
Exp Log P: 3.32
Exp Ref : HANSCH,C ET AL. (1995)

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	12	Aromatic Carbon	0.2940	3.5280
Frag	2	-OH [hydroxy, aromatic attach]	-0.4802	-0.9604
Frag	1	-tert Carbon [3 or more carbon attach]	0.2676	0.2676
Factor	1	>C< (aliphatic), 2 phenyl attach correc	-0.5158	-0.5158
Const		Equation Constant		0.2290
			Log Kow =	3.6430

MPBPVP (v1.43) Program Results:
==========
Experimental Database Structure Match:
Name : DIPHENYLOLPROPANE
CAS Num : 000080-05-7
Exp MP (deg C): 153
Exp BP (deg C): 220 @ 4 mm Hg
Exp VP (mm Hg): ---

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29

---------- SUMMARY MPBVP v1.43 ----------

Boiling Point: 363.54 deg C (Adapted Stein and Brown Method)

Melting Point: 264.35 deg C (Adapted Joback Method)

Melting Point: 98.61 deg C (Gold and Ogle Method)
Mean Melt Pt : 181.48 deg C (Joback; Gold,Ogle Methods)
  Selected MP: 131.76 deg C (Weighted Value)

Vapor Pressure Estimations (25 deg C):
  (Using BP: 363.54 deg C (estimated))
  (Using MP: 153.00 deg C (exp database))
    VP: 7.59E-008 mm Hg (Antoine Method)
      : 1.01E-005 Pa (Antoine Method)
    VP: 2.27E-007 mm Hg (Modified Grain Method)
      : 3.03E-005 Pa (Modified Grain Method)
    VP: 6.81E-006 mm Hg (Mackay Method)
      : 0.000908 Pa (Mackay Method)
  Selected VP: 2.27E-007 mm Hg (Modified Grain Method)
              : 3.03E-005 Pa (Modified Grain Method)
  Subcooled liquid VP: 4.6E-006 mm Hg (25 deg C, Mod-Grain method)
                      : 0.000613 Pa (25 deg C, Mod-Grain method)

TYPE	NUM	BOIL DESCRIPTION	COEFF	VALUE
Group	2	-CH3	21.98	43.96
Group	1	>C<	4.50	4.50
Group	2	-OH (phenol)	70.48	140.96
Group	8	CH (aromatic)	28.53	228.24
Group	4	-C (aromatic)	30.76	123.04
*		Equation Constant		198.18
RESULT-uncorr		BOILING POINT in deg Kelvin		738.88
RESULT- corr		BOILING POINT in deg Kelvin		636.70
		BOILING POINT in deg C		363.54

TYPE	NUM	MELT DESCRIPTION	COEFF	VALUE
Group	2	-CH3	-5.10	-10.20
Group	1	>C<	46.43	46.43
Group	2	-OH (phenol)	82.83	165.66
Group	8	CH (aromatic)	8.13	65.04
Group	4	-C (aromatic)	37.02	148.08
*		Equation Constant		122.50
RESULT		MELTING POINT in deg Kelvin		537.51
		MELTING POINT in deg C		264.35

Water Sol from Kow (WSKOW v1.42) Results:
==========

          Water Sol: 172.7 mg/L

Experimental Water Solubility Database Match:
  Name   : DIPHENYLOLPROPANE
  CAS Num : 000080-05-7
  Exp WSol : 120 mg/L (25 deg C)
  Exp Ref : DORN,PB ET AL. (1987)

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM   : bisphenol-a
MOL FOR: C15 H16 O2

MOL WT : 228.29

---------- WSKOW v1.42 Results ----------

Log Kow (estimated) : 3.64
Log Kow (experimental): 3.32
Cas No: 000080-05-7
Name : DIPHENYLOLPROPANE
Refer : HANSCH,C ET AL. (1995)
Log Kow used by Water solubility estimates: 3.32

Equation Used to Make Water Sol estimate:
Log S (mol/L) = 0.796 - 0.854 log Kow - 0.00728 MW + Correction
(used when Melting Point NOT available)

Correction(s):	Value
Phenol	0.580

Log Water Solubility (in moles/L) : -3.121
Water Solubility at 25 deg C (mg/L): 172.7

WATERNT Program (v1.01) Results:

Water Sol (v1.01 est): 146.15 mg/L

Experimental Water Solubility Database Match:
Name : DIPHENYLOLPROPANE
CAS Num : 000080-05-7
Exp WSol : 120 mg/L (25 deg C)
Exp Ref : DORN,PB ET AL. (1987)

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29

TYPE	NUM	WATER SOLUBILITY FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	-0.3213	-0.6425
Frag	8	Aromatic Carbon (C-H type)	-0.3359	-2.6869
Frag	4	Aromatic Carbon (C-substituent type)	-0.5400	-2.1598
Frag	1	-OH [combined multiple aromatic attach]	2.6237	2.6237
Frag	1	-tert Carbon [3 or more carbon attach]	-0.5774	-0.5774
Const		Equation Constant		0.2492

Log Water Sol (moles/L) at 25 dec C = -3.1937
Water Solubility (mg/L) at 25 dec C = 146.15

ECOSAR Program (v1.00) Results:

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
CAS Num:
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C15 H16 O2
MOL WT : 228.29
Log Kow: 3.64 (KowWin estimate)

Melt Pt:
Wat Sol: 120 mg/L (experimental database)

ECOSAR v1.00 Class(es) Found

Phenols, Poly

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Phenols, Poly	Fish	96-hr	LC50	2.350
Phenols, Poly	Daphnid	48-hr	LC50	5.237
Phenols, Poly	Green Algae	96-hr	EC50	1.389
Phenols, Poly	Fish	30-day	ChV	0.550
Phenols, Poly	Daphnid	21-day	ChV	1.773
Phenols, Poly	Green Algae		ChV	0.227
Neutral Organic SAR (Baseline Toxicity)	Fish	96-hr	LC50	7.160
	Daphnid	48-hr	LC50	5.039
	Green Algae	96-hr	EC50	4.263
	Fish		ChV	0.655
	Daphnid		ChV	0.622
	Green Algae		ChV	2.083

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Phenols, Poly :

For Fish Acute Toxicity Values: If the log Kow of the chemical is greater than 7.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Daphnid Acute Toxicity Values: If the log Kow of the chemical is greater than 5.5, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 7.0 (Fish LC50)
Maximum LogKow: 5.5 (Daphnid LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

HENRYWIN (v3.20) Program Results:
==========

Bond Est : 9.16E-012 atm-m3/mole (9.28E-007 Pa-m3/mole)
Group Est: Incomplete

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29

HENRYWIN v3.20 Results

CLASS		BOND CONTRIBUTION DESCRIPTION	COMMENT	VALUE
HYDROGEN	6	Hydrogen to Carbon (aliphatic) Bonds		-0.7181
HYDROGEN	8	Hydrogen to Carbon (aromatic) Bonds		-1.2344
HYDROGEN	2	Hydrogen to Oxygen Bonds		6.4635
FRAGMENT	2	C-C		0.2326
FRAGMENT	2	C-Car		0.3239
FRAGMENT	12	Car-Car		3.1657
FRAGMENT	2	Car-OH		1.1934
RESULT		BOND ESTIMATION METHOD for LWAPC VALUE	TOTAL	9.427

HENRYs LAW CONSTANT at 25 deg C = 9.16E-012 atm-m3/mole
= 3.74E-010 unitless
= 9.28E-007 Pa-m3/mole

		GROUP CONTRIBUTION DESCRIPTION	COMMENT	VALUE
	2	CH3 (X)		-1.24
	8	Car-H (Car)(Car)		0.88
	2	Car (C)(Car)(Car)		1.40
	2	Car (Car)(Car)(O)		-0.86
	2	O-H (Car)		8.90
		MISSING Value for: C (C)(Car)(Car)(C)		
RESULT		GROUP ESTIMATION METHOD for LOG GAMMA VALUE	INCOMPLETE	9.08

For Henry LC Comparison Purposes:
Exper Database: none available
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 3.948E-010 atm-m3/mole (4.001E-005 Pa-m3/mole)
VP: 2.27E-007 mm Hg (source: MPBPVP)
WS: 173 mg/L (source: WSKOWWIN)

Log Octanol-Air (KOAWIN v1.10) Results:
==========

Log Koa: 12.747

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2

MOL WT : 228.29

---------- KOAWIN v1.10 Results ----------

Log Koa (octanol/air) estimate: 12.747
    Koa (octanol/air) estimate: 5.579e+012
 Using:
   Log Kow: 3.32 (exp database)
   HenryLC: 9.16e-012 atm-m3/mole (HenryWin est)
   Log Kaw: -9.427 (air/water part.coef.)

 LogKow : 3.32 (exp database)
 LogKow : 3.64 (KowWin estimate)
 Henry LC: --- atm-m3/mole(exp database)
 Henry LC: 9.16e-012 atm-m3/mole (HenryWin bond estimate)

 Log Koa (octanol/air) estimate: 13.067 (from KowWin/HenryWin)

BIOWIN (v4.10) Program Results:
==========
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM   : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29

---------- BIOWIN v4.10 Results ----------

   Biowin1 (Linear Model Prediction)   : Biodegrades Fast
   Biowin2 (Non-Linear Model Prediction): Does Not Biodegrade Fast
   Biowin3 (Ultimate Biodegradation Timeframe): Weeks-Months
   Biowin4 (Primary Biodegradation Timeframe): Days-Weeks
   Biowin5 (MITI Linear Model Prediction)   : Does Not Biodegrade Fast
   Biowin6 (MITI Non-Linear Model Prediction): Does Not Biodegrade Fast
   Biowin7 (Anaerobic Model Prediction): Does Not Biodegrade Fast
   Ready Biodegradability Prediction: NO

TYPE	NUM	Biowin1 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	0.1158	0.2316
Frag	1	Carbon with 4 single bonds & no hydrogens	-0.1839	-0.1839
MolWt	*	Molecular Weight Parameter		-0.1087
Const	*	Equation Constant		0.7475
RESULT		Biowin1 (Linear Biodeg Probability)		0.6866

TYPE	NUM	Biowin2 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	0.9086	1.8172
Frag	1	Carbon with 4 single bonds & no hydrogens	-1.7232	-1.7232
MolWt	*	Molecular Weight Parameter		-3.2418
RESULT		Biowin2 (Non-Linear Biodeg Probability)		0.4653

 A Probability Greater Than or Equal to 0.5 indicates --> Biodegrades Fast
 A Probability Less Than 0.5 indicates --> Does NOT Biodegrade Fast

TYPE	NUM	Biowin3 FRAGMENT DESCRIPTION	COEFF	VALUE

Frag	2	Aromatic alcohol [-OH]	0.0564	0.1128
Frag	1	Carbon with 4 single bonds & no hydrogens	-0.2121	-0.2121
MolWt	*	Molecular Weight Parameter		-0.5045
Const	*	Equation Constant		3.1992
RESULT		Biowin3 (Survey Model - Ultimate Biodeg)		2.5953

TYPE	NUM	Biowin4 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	0.0397	0.0794
Frag	1	Carbon with 4 single bonds & no hydrogens	-0.1534	-0.1534
MolWt	*	Molecular Weight Parameter		-0.3294
Const	*	Equation Constant		3.8477
RESULT		Biowin4 (Survey Model - Primary Biodeg)		3.4443

Result Classification: 5.00 -> hours 4.00 -> days 3.00 -> weeks
(Primary & Ultimate) 2.00 -> months 1.00 -> longer

TYPE	NUM	Biowin5 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	0.0642	0.1285
Frag	1	Carbon with 4 single bonds & no hydrogens	0.0676	0.0676
Frag	8	Aromatic-H	0.0082	0.0657
Frag	2	Methyl [-CH3]	0.0004	0.0008
MolWt	*	Molecular Weight Parameter		-0.6792
Const	*	Equation Constant		0.7121
RESULT		Biowin5 (MITI Linear Biodeg Probability)		0.2956

TYPE	NUM	Biowin6 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	0.4884	0.9768
Frag	1	Carbon with 4 single bonds & no hydrogens	0.3990	0.3990
Frag	8	Aromatic-H	0.1201	0.9611
Frag	2	Methyl [-CH3]	0.0194	0.0389
MolWt	*	Molecular Weight Parameter		-6.5905
RESULT		Biowin6 (MITI Non-Linear Biodeg Probability)		0.1559

A Probability Greater Than or Equal to 0.5 indicates --> Readily Degradable
A Probability Less Than 0.5 indicates --> NOT Readily Degradable

TYPE	NUM	Biowin7 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	0.0807	0.1614
Frag	1	Carbon with 4 single bonds & no hydrogens	-0.3342	-0.3342
Frag	8	Aromatic-H	-0.0954	-0.7634
Frag	2	Methyl [-CH3]	-0.0796	-0.1591
Const	*	Equation Constant		0.8361
RESULT		Biowin7 (Anaerobic Linear Biodeg Prob)		-0.2593

```
 A Probability Greater Than or Equal to 0.5 indicates --> Biodegrades Fast
 A Probability Less Than 0.5 indicates --> Does NOT Biodegrade Fast

Ready Biodegradability Prediction: (YES or NO)
----------------------------------------------
 Criteria for the YES or NO prediction:  If the Biowin3 (ultimate survey
 model) result is "weeks" or faster (i.e. "days", "days to weeks", or
 "weeks" AND the Biowin5 (MITI linear model) probability is >= 0.5, then
 the prediction is YES (readily biodegradable).  If this condition is not
 satisfied, the prediction is NO (not readily biodegradable).  This method
 is based on application of Bayesian analysis to ready biodegradation data
 (see Help).  Biowin5 and 6 also predict ready biodegradability, but for
 degradation in the OECD301C test only; using data from the Chemicals
 Evaluation and Research Institute Japan (CERIJ) database.



BioHCwin (v1.01) Program Results:
=================================
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM   : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29
-------------------------- BioHCwin v1.01 Results --------------------------

  NO Estimate Possible ... Structure NOT a Hydrocarbon
    (Contains atoms other than C, H or S (-S-))



AEROWIN Program (v1.00) Results:
================================
 Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
  Vapor pressure (liquid/subcooled):  0.000613 Pa (4.6E-006 mm Hg)
  Log Koa (Koawin est  ): 12.747
   Kp (particle/gas partition coef. (m3/ug)):
       Mackay model           :  0.00489
       Octanol/air (Koa) model:  1.37
   Fraction sorbed to airborne particulates (phi):
       Junge-Pankow model     :  0.15
       Mackay model           :  0.281
       Octanol/air (Koa) model:  0.991


AOP Program (v1.92) Results:
============================
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM   : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29
------------------- SUMMARY (AOP v1.92): HYDROXYL RADICALS (25 deg C) --------
Hydrogen Abstraction       =   0.3346 E-12 cm3/molecule-sec
Reaction with N, S and -OH =   0.2800 E-12 cm3/molecule-sec
Addition to Triple Bonds   =   0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds =   0.0000 E-12 cm3/molecule-sec
**Addition to Aromatic Rings =  79.9632 E-12 cm3/molecule-sec
Addition to Fused Rings    =   0.0000 E-12 cm3/molecule-sec

   OVERALL OH Rate Constant =  80.5777 E-12 cm3/molecule-sec
   HALF-LIFE =     0.133 Days (12-hr day; 1.5E6 OH/cm3)
   HALF-LIFE =     1.593 Hrs
.......................  ** Designates Estimation(s) Using ASSUMED Value(s)
```

```
------------------- SUMMARY (AOP v1.91): OZONE REACTION (25 deg C) -----------

               ******  NO OZONE REACTION ESTIMATION ******
               (ONLY Olefins and Acetylenes are Estimated)

 NOTE: Reaction with Nitrate Radicals May Be Important!

Experimental Database:  NO Structure Matches
Fraction sorbed to airborne particulates (phi):
  0.216 (Junge-Pankow, Mackay avg)
  0.991 (Koa method)
     Note: the sorbed fraction may be resistant to atmospheric oxidation



KOCWIN Program (v2.00) Results:
==============================
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM   : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29
--------------------------  KOCWIN v2.00 Results  --------------------------

  Koc Estimate from MCI:
  ----------------------
        First Order Molecular Connectivity Index  ..... :  7.998
        Non-Corrected Log Koc (0.5213 MCI + 0.60)  ..... :  4.7692
        Fragment Correction(s):
                 2   Aromatic Hydroxy (aromatic-OH)  .....  : -0.1932
        Corrected Log Koc  ............................... :  4.5760

                        Estimated Koc:  3.767e+004  L/kg   <===========

  Koc Estimate from Log Kow:
  --------------------------
        Log Kow  (experimental DB)  ....................... :  3.32
        Non-Corrected Log Koc (0.55313 logKow + 0.9251)  .... :  2.7615
        Fragment Correction(s):
                 2   Aromatic Hydroxy (aromatic-OH)  .....  :  0.3337
        Corrected Log Koc  ............................... :  3.0952

                        Estimated Koc:  1245  L/kg   <===========



HYDROWIN Program (v2.00) Results:
================================
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM   : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29
-------------------------- HYDROWIN v2.00 Results --------------------------


 Currently, this program can NOT estimate a hydrolysis rate constant for
                the type of chemical structure entered!!

 ONLY Esters, Carbamates, Epoxides, Halomethanes (containing 1-3 halogens),
      Specific Alkyl Halides & Phosphorus Esters can be estimated!!

   When present, various hydrolyzable compound-types will be identified.
```

For more information, (Click OVERVIEW in Help or see the User's Guide)

***** CALCULATION NOT PERFORMED *****

BCFBAF Program (v3.01) Results:
==========
SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : bisphenol-a
MOL FOR: C15 H16 O2
MOL WT : 228.29
---------- BCFBAF v3.01 ----------
Summary Results:
Log BCF (regression-based estimate): 1.86 (BCF = 72 L/kg wet-wt)
Biotransformation Half-Life (days) : 0.263 (normalized to 10 g fish)
Log BAF (Arnot-Gobas upper trophic): 2.24 (BAF = 173 L/kg wet-wt)

Experimental BCF-kM Database Structure Match:

Name : Phenol, 4,4 -(1-methylethylidene)bis-
CAS Num : 000080-05-7
Log BCF : 1.6415 (BCF = 43.8 L/kg wet-wt)
BCF Data : BCF NonIonic Training Set
Log Bio HL: 0.271 (Bio Half-life = 1.87 days)
Bio Data : kM Training Set

Log Kow (experimental): 3.32
Log Kow used by BCF estimates: 3.32

Equation Used to Make BCF estimate:
Log BCF = 0.6598 log Kow - 0.333 + Correction

Correction(s): Value
No Applicable Correction Factors

Estimated Log BCF = 1.858 (BCF = 72.03 L/kg wet-wt)

==========
Whole Body Primary Biotransformation Rate Estimate for Fish:
==========

TYPE	NUM	LOG BIOTRANSFORMATION FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	Aromatic alcohol [-OH]	-0.4727	-0.9455
Frag	1	Carbon with 4 single bonds & no hydrogens	-0.2984	-0.2984
Frag	8	Aromatic-H	0.2664	2.1310
Frag	2	Methyl [-CH3]	0.2451	0.4902
Frag	2	Benzene	-0.4277	-0.8555
L Kow	*	Log Kow = 3.32 (experimental)	0.3073	1.0204
MolWt	*	Molecular Weight Parameter		-0.5854
Const	*	Equation Constant		-1.5058
RESULT		LOG Bio Half-Life (days)		-0.5802
RESULT		Bio Half-Life (days)		0.2629
NOTE		Bio Half-Life Normalized to 10 g fish at 15 deg C		

Biotransformation Rate Constant:
kM (Rate Constant): 2.637 /day (10 gram fish)
kM (Rate Constant): 1.483 /day (100 gram fish)
kM (Rate Constant): 0.8338 /day (1 kg fish)
kM (Rate Constant): 0.4689 /day (10 kg fish)

```
Note: For Arnot-Gobas BCF & BAF Methods, Experimental Km Half-Life Used:
   Exp Km Half-Life = 0.271 days (Rate Constant = 0.3714/ day)
Arnot-Gobas BCF & BAF Methods (including biotransformation rate estimates):
   Estimated Log BCF (upper trophic) =  2.237  (BCF = 172.7 L/kg wet-wt)
   Estimated Log BAF (upper trophic) =  2.238  (BAF = 172.8 L/kg wet-wt)
   Estimated Log BCF (mid trophic)   =  2.102  (BCF = 126.5 L/kg wet-wt)
   Estimated Log BAF (mid trophic)   =  2.103  (BAF = 126.8 L/kg wet-wt)
   Estimated Log BCF (lower trophic) =  2.055  (BCF = 113.4 L/kg wet-wt)
   Estimated Log BAF (lower trophic) =  2.058  (BAF = 114.4 L/kg wet-wt)

Arnot-Gobas BCF & BAF Methods (assuming a biotransformation rate of zero):
   Estimated Log BCF (upper trophic) =  2.348  (BCF = 222.7 L/kg wet-wt)
   Estimated Log BAF (upper trophic) =  2.454  (BAF = 284.5 L/kg wet-wt)
```

Volatilization From Water

Chemical Name: bisphenol-a

```
Molecular Weight    :  228.29 g/mole
Water Solubility    :  -----
Vapor Pressure      :  -----
Henry's Law Constant:  9.16E-012 atm-m3/mole  (estimated by Bond SAR Method)
```

	RIVER	LAKE
Water Depth (meters):	1	1
Wind Velocity (m/sec):	5	0.5
Current Velocity (m/sec):	1	0.05
HALF-LIFE (hours) :	9.657E+007	1.054E+009
HALF-LIFE (days) :	4.024E+006	4.39E+007
HALF-LIFE (years) :	1.102E+004	1.202E+005

STP Fugacity Model: Predicted Fate in a Wastewater Treatment Facility

(using 10000 hr Bio P,A,S)

PROPERTIES OF: bisphenol-a

Molecular weight (g/mol)	228.29
Aqueous solubility (mg/l)	0
Vapour pressure (Pa)	0
(atm)	0
(mm Hg)	0
Henry 's law constant (Atm-m3/mol)	9.16E-012
Air-water partition coefficient	3.74617E-010
Octanol-water partition coefficient (Kow)	2089.3
Log Kow	3.32
Biomass to water partition coefficient	418.659
Temperature [deg C]	25

Biodeg rate constants (h^-1),half life in biomass (h) and in 2000 mg/L MLSS (h):

-Primary tank	0.00	4557.29	10000.00
-Aeration tank	0.00	4557.29	10000.00
-Settling tank	0.00	4557.29	10000.00

STP Overall Chemical Mass Balance:

	g/h	mol/h	percent
Influent	1.00E+001	4.4E-002	100.00
Primary sludge	4.86E-001	2.1E-003	4.86
Waste sludge	4.53E-001	2.0E-003	4.53
Primary volatilization	4.61E-009	2.0E-011	0.00
Settling volatilization	1.25E-008	5.5E-011	0.00
Aeration off gas	3.07E-008	1.3E-010	0.00
Primary biodegradation	2.98E-003	1.3E-005	0.03
Settling biodegradation	8.85E-004	3.9E-006	0.01
Aeration biodegradation	1.16E-002	5.1E-005	0.12
Final water effluent	9.05E+000	4.0E-002	90.46
Total removal	9.54E-001	4.2E-003	9.54
Total biodegradation	1.55E-002	6.8E-005	0.16

Level III Fugacity Model (Full-Output):

Chem Name : bisphenol-a
Molecular Wt: 228.29
Henry's LC : 9.16e-012 atm-m3/mole (Henrywin program)
Vapor Press : 2.27e-007 mm Hg (Mpbpwin program)
Liquid VP : 2.58e-006 mm Hg (super-cooled)
Melting Pt : 132 deg C (Mpbpwin program)
Log Kow : 3.32 (Kowwin program)
Soil Koc : 3.77e+004 (KOCWIN MCI method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	7.59e-005	3.18	1000
Water	8.31	900	1000
Soil	74.1	1.8e+003	1000
Sediment	17.6	8.1e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	4.01e-015	1.1	0.0505	0.0366	0.00168
Water	1.05e-016	425	553	14.2	18.4
Soil	1.21e-017	1.9e+003	0	63.2	0
Sediment	1.3e-016	100	23.4	3.34	0.781

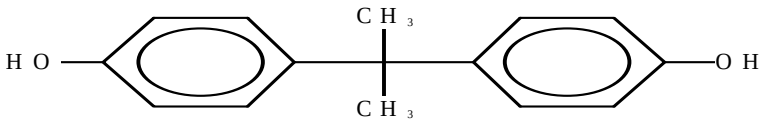
Persistence Time: 2.22e+003 hr
Reaction Time: 2.74e+003 hr
Advection Time: 1.15e+004 hr
Percent Reacted: 80.8
Percent Advected: 19.2

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 3.185
Water: 900
Soil: 1800
Sediment: 8100
Biowin estimate: 2.595 (weeks-months)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Appendix 2
ECOSAR Modeling Results – Bisphenol-A

- **ECOSAR Results for Chemical Name (CAS #80-05-7)**



ECOSAR Version 1.11 Results Page

SMILES : CC(C)(c1ccc(cc1)O)c2ccc(cc2)O
CHEM : Bisphenol a
CAS Num: 80-05-7
ChemID1:
MOL FOR: C15 H16 O2
MOL WT : 228.29
Log Kow: 3.643 (EPISuite Kowwin v1.68 Estimate)
Log Kow: (User Entered)
Log Kow: 3.32 (PhysProp DB exp value - for comparison only)
Melt Pt: (User Entered for Wat Sol estimate)
Melt Pt: 153.00 (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 85.28 (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol: (User Entered)
Wat Sol: 120 (mg/L, PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log Kow: 3.643 (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 120 (mg/L, PhysProp DB exp value)

Available Measured Data from ECOSAR Training Set

CAS No	Organism	Duration	End Pt	Measured mg/L (ppm)	Ecosar Class	Reference
000080-05-7	Algae (SW)	96-hr	EC50	1	Phenols, poly	Soc. Plastics I
000080-05-7	Mysid	96-hr	LC50	1.1	Phenols, poly	Soc. Plastics I
000080-05-7	Green Algae	96-hr	EC50	2.5	Phenols, poly	Soc. Plastics I
000080-05-7	Green Algae	96-hr	EC50	2.7	Phenols, poly	Alexander et al
000080-05-7	Daphnid	48-hr	LC50	3.9	Phenols, poly	Soc. Plastics I
000080-05-7	Fish	96-hr	LC50	4.6	Phenols, poly	Alexander et al
000080-05-7	Fish	96-hr	LC50	4.7	Phenols, poly	Alexander et al
000080-05-7	Fish (SW)	96-hr	LC50	7.5	Phenols, poly	Soc. Plastics I
000080-05-7	Fish (SW)	96-hr	LC50	9.4	Phenols, poly	Soc. Plastics I
000080-05-7	Daphnid	48-hr	LC50	10.2	Phenols, poly	Alexander et al

---
ECOSAR v1.11 Class-specific Estimations

Phenols, Poly

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Phenols, Poly	: Fish	96-hr	LC50	1.284
Phenols, Poly	: Daphnid	48-hr	LC50	5.237
Phenols, Poly	: Green Algae	96-hr	EC50	1.331
Phenols, Poly	: Fish		ChV	0.550

Phenols, Poly	: Daphnid		ChV	1.773
Phenols, Poly	: Green Algae		ChV	0.227

Neutral Organic SAR	: Fish	96-hr	LC50	6.274
(Baseline Toxicity)	: Daphnid	48-hr	LC50	4.146
	: Green Algae	96-hr	EC50	5.782
	: Fish		ChV	0.733
	: Daphnid		ChV	0.617
	: Green Algae		ChV	2.123

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Phenols, Poly :

Maximum LogKow: 7.0 (Fish LC50)
Maximum LogKow: 5.5 (Daphnid LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

Appendix C

Alternatives Summary Table

BPA Application	Example of BPA Product	BPA Alternatives Considered	Preferred BPA Alternative	Alternative Packaging Currently in Use	Alternative Product Photo
Liquid infant formula containers	Mead Johnson (Enfamil) sells "ready-to-feed" infant formula in aluminum cans lined with BPA coating.	Liquid formula packaged in: • Plastic bottles (PP, PET, HDPE, Tritan Copolyester™) • Cans with polyester coatings (e.g., DAREX Polyester), PET film, baked-on resins (e.g., Oleoresin), or corn-based isosorbide diglycidyl ether liners (under patent, developed by New Jersey Institute of Technology [NJIT])	Liquid formula packaged in: • Plastic bottles (PP, PET, HDPE). Ranking in order of preference: 1. PP 2. PE options Rationale: The other considered alternatives are not currently used in infant formula packaging and may not be suitable due to limited information/uncertainties (e.g., isosorbide liners), function, recyclability, or other factors. For example, Tritan Copolyester™ may be an option for reusable sippy cups and bottles, but is not likely cost-effective for single-use formula containers. In addition, further study is necessary regarding isosorbide liners.	Examples: Similac, as well as many other liquid formula producers, have switched to plastic bottles instead of aluminum cans	X
Baby Food containers	Glass baby food jars with lids containing BPA epoxy coatings to seal the jars	Baby food packaged in: • Plastic containers (PP, PET, HDPE, PS, PLA) • Glass jars with lids (e.g., DAREX Polyester,), PET film, baked-on resins (e.g., Oleoresin), or isosorbide liners (under patent, developed by NJIT) • Aseptic containers and paperboard, which consists of approximately 70% paper, 24% PE, and 6% aluminum • Laminated pouches with PP or PE as the food contact surface	All of the considered options are considered suitable alternatives. Ranking in order of preference: 1. PP containers 2. PE containers 3. PLA containers 4. PE-lined PS containers 5. Glass jars with PE-coated lids 6. Aseptic containers 7. Laminated pouches 8. Cans lined with baked-on resins or isosorbide liners (more research is needed) Rationale: All are considered non-toxic alternatives to BPA. Recyclability is considered the secondary consideration in the ranking.	Examples: Gerber baby food plastic containers are made from #1 (PET) and #6 (PS) layered plastic. In addition, aseptic containers like Tetra Pak and laminated pouches like Cheer Pack.	X

References: Guzman 2010, Pierce and Caliendo 2012, USDHHS 2012

Appendix D

GreenScreen Version 1.2 Assessment Template

GreenScreen™ Assessment for [*Chemical Name (CAS #)*]

GreenScreen™ Version 1.2 Draft Assessment
Note: Validation Has Not Been Performed on this Green Screen Assessment

Chemical Name:

Green Screen Assessment Prepared By:
Name:
Title:
Organization:
Date:

Quality Control Performed By:
Name:
Title:
Organization:
Date:

Confirm application of the *de minimus* rule[3]: (if no, what *de minimus* did you use?)

Chemical Name (CAS #):

Also Called:

Chemical Surrogates, analogs or moieties used in this assessment (CASs #):

Chemical Structure(s):
*Note: Include chemical structure(s) of all surrogates, analogs (and /or moieties) used in the assessment.

Notes related to production specific attributes[4]:

For Inorganic Chemicals and relevant particulate organics (*if not relevant, list NA*)
Define Properties:
1. Particle size (e.g. silica of respirable size)
2. Structure (e.g. amorphous vs. crystalline)
3. Mobility (e.g. Water solubility, volatility)
4. Bioavailability

For Polymers: (*delete this section if not a polymer*)
Identify Monomers and Corresponding Properties
1. % of Each Monomer
   a) Monomer 1
   b) Monomer 2
   c) Monomer 3
2. Are the monomers blocked? (Y/N)
3. Molecular Weight (MW) of Polymer
4. % of Polymer with
   a) MW <500
   b) MW <1,000
5. % Weight Residual Monomers
6. Solubility/Dispersability/Swellability
7. Particle Size
8. Overall Polymer Charge
9. Identify constituents and residual concentrations of
   a) Catalysts
   b) Processing aids

Identify Applications/Functional Uses:
(e.g. Cleaning product, TV casing)
1.
2.

[3] Every chemical in a material or formulation should be assessed if it is:

1. intentionally added and/or
2. present at greater than or equal to 100 ppm.

[4] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen assessment of the generic chemical by CAS #.

Green Screen Rating[5]: [*Chemical name*] was assigned a Benchmark Score of [*#*] based on ... [*add rationale*].

Green Screen Hazard Ratings: [*Chemical Name*]																		
Group I Human					Group II and II* Human										Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE		AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*											

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values and lower confidence. Hazard levels in **BOLD** font reflect values based on test data (See Guidance).

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[6]

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	On CPA Red List[7]?	Green Screen Rating[8]

Introduction

Hazard Classification Summary Section:
Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for carcinogenicity based on [*describe results relative to criteria*].
Indicate if a surrogate was used.
Summary, value and references[9]

Mutagenicity/Genotoxicity (M) Score (H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for mutagenicity based on [*describe results relative to criteria*].
Indicate if a surrogate was used.
Summary, value and references

Reproductive Toxicity (R) Score (H, M, or L):

[5] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[6] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

[7] The CPA "Red List" refers to chemicals 1. flagged as Benchmark 1 using the GreenScreen™ List Translator or 2. flagged as Benchmark 1 or 2 using the GreenScreen™ List Translator and further assessed and assigned as Benchmark 1. The most recent version of the GreenScreen™ List Translator should be used.

[8] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

[9] Note that alternatively, references may placed at end

[*Chemical name*] was assigned a score of [*Score*] for reproductive toxicity based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for developmental toxicity based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Endocrine Activity (E) Score (H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for endocrine activity based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Group II and II* Human Health Effects (Group II and II* Human)
Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for acute mammalian toxicity based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
Group II Score (single dose: vH, H, M or L);
[*Chemical name*] was assigned a score of [*Score*] for systemic toxicity/organ effects based on single exposure [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Group II* Score (repeated dose: H, M, L):
[*Chemical name*] was assigned a score of [*Score*] for systemic toxicity/organ effects based on repeated exposure [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Neurotoxicity (N)
Group II Score (single dose: vH, H, M or L)
[*Chemical name*] was assigned a score of [*Score*] for neurotoxicity based on single exposure [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Group II* Score (repeated dose: H, M, L):
[*Chemical name*] was assigned a score of [*Score*] for neurotoxicity based on repeated exposure [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Skin Sensitization (SnS) Group II* Score (H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for skin sensitization based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Respiratory Sensitization (SnR) Group II* Score (H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for respiratory sensitization based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for skin irritation/corrosivity based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for eye irritation/corrosivity based on [*describe results relative to criteria*]. Indicate if a surrogate was used.
Summary, value and references

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for acute aquatic toxicity based on [*describe results relative to criteria*]. Indicate which species and if a surrogate was used.
Summary, value and references

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for chronic aquatic toxicity based on [*describe results relative to criteria*]. Indicate which species and if a surrogate was used.
Summary, value and references

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL):
[*Chemical name*] was assigned a score of [*Score*] for persistence based on [*describe results relative to criteria*]. Indicate which species and if a surrogate was used.
Summary, value and references

Bioaccumulation (B) Score (vH, H, M, L, or vL):
[*Chemical name*] was assigned a score of [*Score*] for bioaccumulation based on [*describe results relative to criteria*]. Indicate which species and if a surrogate was used.
Summary, value and references

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for reactivity based on [*describe results relative to criteria*]. Indicate which species and if a surrogate was used.
Summary, value and references

Flammability (F) Score (vH, H, M or L):
[*Chemical name*] was assigned a score of [*Score*] for flammability based on [*describe results relative to criteria*]. Indicate which species and if a surrogate was used.
Summary, value and references

References (may be provided under each hazard endpoint or at the end of document)

Appendix X[10]
Modeling Results

Attach:

- **EPISuite Results for Chemical Name (CAS #)**
- **ECOSAR Results for Chemical Name (CAS #)**
- **Other**

[10] Attach separate Appendix for each set of modeling results