Risk-Based Green Screen Assessment of Bisphenol A

Prepared for

John M. Rost, PhD
CROWN Packaging - Crown Technology
Crown Holdings, Inc.
11535 S. Central Ave
Alsip, IL 60803

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Gradient
www.gradientcorp.com
Science and Strategies for Health and the Environment

20 University Road
Cambridge, MA 02138
617-395-5000

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Abbreviations

BPA	Bisphenol A
EC_{10}	Effect Concentration for 10% of the population tested
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization
JECFA	Joint FAO/WHO Expert Committee
LC_{50}	Lethal Concentration for 50% of the population tested
LD_{50}	Lethal Dose for 50% of the population tested
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
WHO	World Health Organization

1 Introduction

Clean Production Action conducted a Green Screen for Bisphenol A (BPA) in 2007 in which it assessed multiple human health and ecological hazard categories (Rossi and Heine, 2007). This analysis was based primarily on a risk assessment conducted by the European Union in 2003 and a select few more recent studies. The Green Screen characterized high, moderate, and low "levels of concern" based on pre-determined thresholds for these categories. Based on the levels of concern for each hazard category, it was determined whether BPA met a set of hazard criteria for any of four benchmarks that define a "progressively safer chemical."

In Clean Production Action's hazard-based analysis, it was concluded that BPA did not pass the Benchmark 1 criteria because there was a high level of concern for endocrine disruption, as well as emerging evidence of potentially high concern for reproductive and developmental effects. While hazard indicates the potential for an adverse effect, if exposure is low, a substance with a high hazard will be associated with low risk. Thus, an exposure evaluation is a critical component of assessing human health or ecological risk.

We conducted a modified Green Screen of BPA that focuses on assessing risks rather than hazards. We incorporated information on exposure and dose in the determination of levels of concern for each risk category. We ranked the levels of concern as high, moderate, and low. Our evaluation is based primarily on evaluations conducted by government agencies and systematic critical reviews in the peer-reviewed literature. We also considered original research studies conducted more recently than these reviews that were conducted using scientifically robust methodology.

2 Methods

The Green Screen evaluates several categories for potential human health, ecological, and environmental effects (Table 1). The categories of carcinogenicity, genotoxicity/mutagenicity, reproductive toxicity, developmental toxicity, endocrine disruption, and neurotoxicity are considered priority health effects for evaluation of the benchmark criteria of the Green Screen. In addition, the physical/chemical properties of flammability and explosiveness are evaluated for the benchmark criteria.

Table 1 Green Screen Categories for Assessment

Human Health	Ecological	Environmental
Carcinogenicity	Acute Aquatic	Bioaccumulation Potential
Genotoxicity/Mutagenicity	Chronic Aquatic	Persistence
Reproductive Toxicity		
Developmental Toxicity		
Endocrine Disruption		
Neurotoxicity		
Immunotoxicity		
Acute Toxicity		
Systemic/Organ Toxicity		
Skin Sensitization		
Respiratory Irritation/Sensitization		
Skin Irritation/Corrosion		
Eye Irritation/Corrosion		

After evaluation, each category is divided into three levels of concern: low, moderate, and high (although the environmental categories of persistence and bioaccumulation include an additional level of "very high" concern in the Green Screen). The level of concern for each category is defined by hazard-based threshold values developed for the Green Screen (Rossi and Heine, 2007). We determined the levels of concern for each category using a weight-of-evidence approach that was modified to consider both hazard and exposure. We based these determinations on evaluations conducted by government agencies and systematic critical reviews in the peer-reviewed literature, as well as original research studies identified through literature searches of the PubMed database. Categories that had a low level of concern based on hazard are indicative of a low level of concern for risk as well, because a low hazard potential indicates a low risk, regardless of exposure. For categories that were above a low level of concern based on hazard, we incorporated information on exposure to conduct a risk-based evaluation.

We then determined which benchmark criteria were met, as described in Figure 2 of Rossi and Heine (2007) and presented in Table 2, below, except that we defined "toxicity" as a function of hazard and exposure (*i.e.*, risk), and not just hazard alone.

Table 2 Green Screen Benchmarks for Progressively Safer Chemicals

Benchmark	Definition	Criteria
1	Avoid – Chemical of high concern	a. High P + high B + high T (high human toxicity or ecotoxicity) b. Very high P + very high B c. (Very high P + high T) or (very high B + high T) d. High human toxicity for any priority effect
2	Use, but search for safer substitutes	a. Moderate P + moderate B + moderate T (moderate human toxicity or ecotoxicity) b. High P + high B c. (High P + moderate T) or (high B + moderate T) d. Moderate human toxicity for any priority effect or high human toxicity e. High flammability or explosiveness
3	Use, but still opportunity for improvement	a. Moderate P or moderate B b. Moderate ecotoxicity c. Moderate human toxicity d. Moderate flammability or explosiveness
4	Prefer – Safer chemical	Low P + low B + low human toxicity + low ecotoxicity

Abbreviations: B = bioaccumulation; P = persistence; T = human toxicity and ecotoxicity (based on risk).

3 BPA Levels of Concern

We used a weight-of-evidence approach to evaluate the potential for BPA toxicity among the effect categories. For effect categories that were judged to have more than a low level of concern based on hazard, we evaluated doses used in the available studies to assess the level of concern for risk. Below, current human exposures are reviewed, followed by the evaluation of BPA evidence and determination of levels of concern.

3.1 Current Human Exposures

Almost all non-occupational human exposures to BPA occur *via* residues in food or beverages that have been in contact with polycarbonate plastic or with containers lined with epoxy resins, as these products can contain trace amounts of the original compound or additional BPA that may be generated during the breakdown of the product (EU, 2003; JECFA, 2010). Oral and dermal exposures can also occur from contact with other products made with BPA. Exposures in the general population are quite low, and often close to or below laboratory detection limits, and the range of exposures among people is small. Estimates based on recent studies of urine measurements indicate that BPA exposures in the US and worldwide generally range from 0.01-0.05 µg/kg-day for adults and 0.02-0.12 µg/kg-day for children (Geens *et al.*, 2012). The 95th percentile exposure estimates for BPA in the general population are 0.27 µg/kg-day and are higher for infants (0.45-1.61 µg/kg-day) and 3- to 5-year-old children (0.78 µg/kg-day) (Geens *et al.*, 2012). In an experimental study where adult volunteers consumed meals comprised of food from epoxy-lined cans over a 24-hour period, the average BPA consumption was estimated from urinary BPA measurements as an average of 0.27 µg/kg and a range of 0.03-0.86 µg/kg (Teeguarden *et al.*, 2011). Urinary measurements are comprised largely of conjugated, biologically inactive BPA, and blood measurements in most studies are most likely due to contamination and are not reflective of actual exposure (Teeguarden *et al.*, 2011).

Two recent studies by the United States Food and Drug Administration (US FDA) indicate that both adult and newborn experimental animals have the capacity to metabolize and eliminate BPA from the body, although there are some species-specific differences. The first study examined this process in rats and found that, after ingesting BPA, adult rats could efficiently and rapidly metabolize and eliminate the chemical, but metabolism in newborn rats was not as efficient. The second study was conducted in monkeys. US FDA found that adult monkeys could efficiently metabolize BPA, and that newborn monkeys had the same capacity as adult monkeys to safely metabolize and eliminate BPA (Doerge *et al.*, 2010a,b). Thus, the authors concluded that effects based on doses in rodent studies over-predicted effects in primates.

3.2 Human Health Effect Assessment

3.2.1 Carcinogenicity

Several researchers have examined whether BPA could be carcinogenic *via* a hormonal mode of action. BPA was first tested for carcinogenicity by the US National Toxicology Program (NTP), which concluded that there was no convincing evidence that BPA was carcinogenic in F344 rats or B6C3F1

mice of either sex (NTP, 1982). In these assays, rats and mice were exposed to dietary BPA for 103 weeks, but not prenatally or during early life.

No government or international organizations classify BPA as a carcinogen. NTP did not list BPA as a carcinogen in the 12th edition of its *Report on Carcinogens* (NTP, 2011) and BPA is not classified as a carcinogen by the International Agency for Research on Cancer, a division of the World Health Organization (WHO). BPA is not listed as a carcinogen in the United States Environmental Protection Agency's (US EPA) Integrated Risk Information System (US EPA, 2012a). Based on the results of the NTP study discussed above, the European Union (EU) also concluded that BPA does not have carcinogenic potential (EU, 2008). BPA is not listed as a chemical known to the state of California to cause cancer under California's Proposition 65 (Cal EPA, 2012). Moreover, in 2002, a panel of prominent scientists conducted a weight-of-evidence evaluation of potential BPA carcinogenicity and concluded that "BPA is not likely to be carcinogenic to humans," citing the NTP bioassay as providing "no substantive evidence to indicate that BPA is carcinogenic to rodents" (Haighton *et al.*, 2002). WHO (2010) concluded that there is currently insufficient evidence on which to judge the carcinogenic potential of BPA. The EU and European Food Safety Authority (EFSA) concluded that of the studies examining potential carcinogenic and/or promoting effects of BPA, none support evidence for carcinogenic potential (EU, 2008; EFSA, 2006).

In the last decade, several non-oral studies have examined the association between BPA and certain precursors to cancer (Timms *et al.*, 2005; Moral *et al.*, 2008; Vandenberg *et al.*, 2007; Wadia *et al.*, 2007). While some of these studies reported associations between BPA and these precursors, none actually reported cancer. These non-oral studies employed injection of BPA as the dosing route, which makes any results of questionable relevance to humans, who are exposed mainly by ingestion. Human oral exposures are subject to first-pass detoxification that is bypassed in injection exposures (Goodman *et al.*, 2009; Hengstler *et al.*, 2011). Consequently, internal doses from the non-oral exposure route in these studies are higher than humans would experience based on the same exposure. Other non-oral studies evaluated BPA in conjunction with other chemical exposures, and while some animals developed mammary (Jenkins *et al.*, 2009) or prostate (Ho *et al.*, 2006) tumors in these studies, these results are also of questionable relevance to humans owing to the co-exposures. These studies also had limitations such as small sample size, use of a single dose level (and, hence, no dose-response information), and lack of information on the background variation of precursor lesions (Ho *et al.*, 2006). Thus, these findings do not indicate that BPA is a human carcinogen.

Together, the evidence indicates that there is **low** concern for the carcinogenicity of BPA.

3.2.2 Genotoxicity/ Mutagenicity

Studies conducted by the NTP to assess the potential of BPA to induce mutations, chromosomal aberrations, sister chromatid exchanges, and transformation in a variety of *in vitro* test systems are largely negative, including studies with *Salmonella typhimurium*, Chinese hamster V79 cells, Syrian hamster embryo cells and mouse lymphoma cells (NTP, 2008a). Recent studies of meiotic abnormalities and aneugenic effects (Hunt *et al.*, 2003; Susiarjo *et al.*, 2007; Pacchierotti, *et al.*, 2008) form the basis for NTP (2008a), Joint Food and Agriculture Organization(FAO)/WHO Expert Committee (JECFA) (2010), and the EU (2008) to conclude that BPA is not likely to pose a genotoxic or mutagenic hazard to humans.

Together, the evidence indicates that there is **low** concern for the genotoxicity or mutagenicity of BPA.

3.2.3 Reproductive Toxicity

Based on hundreds of animal studies with BPA doses ≤ 5 mg/kg-day, there is an overwhelming preponderance of lack-of-effect findings compared to findings of effect over a wide variety of reproductive toxicity endpoints (reviewed by Gray *et al.*, 2004; Goodman *et al.*, 2006, 2009; Hengstler *et al.*, 2011; and multiple government agencies). The most robust reproductive evaluations are the multi-generation studies conducted with Sprague-Dawley rats (Ema *et al.*, 2001; Tyl *et al.*, 2002) and CD-1 Swiss mice (Tyl *et al.*, 2008). These studies utilized a large number of animals with a range of oral doses and examined a wide variety of hormonally sensitive endpoints. Reproductive effects occurred only at the highest tested doses (*e.g.*, 500 or 600 mg/kg-day) in these studies (EFSA, 2010). Effects at lower doses were observed only sporadically (*e.g.*, in only one generation, with no dose-response pattern) and were not considered to be treatment related. It should be noted that even the low doses in these studies are generally orders of magnitude higher than human exposures.

Among all other BPA low-dose animal studies, there are some that reported responses at low doses, but no marked or consistently repeatable effects were observed. Reported effects are not consistent between rats and mice and there are no consistent patterns among dose groups and evaluation times (*e.g.*, Nagel *et al.*, 1997; Gupta, 2000; Ashby *et al.*, 1999; Cagen *et al.*, 1999; Toyama and Yuasa, 2004; Toyama *et al.*, 2004; Tyl *et al.*, 2008). Considered together, the reported effects lack any common pattern consistent with a hormonal mode of action.

NTP used a qualitative five-point scale (*i.e.*, negligible concern, minimal concern, some concern, concern, and serious concern) to describe its conclusions regarding whether and the degree to which evidence indicates that exposure to a substance causes reproductive effects in humans (NTP, 2008a). Based on this scale, NTP defined "negligible concern" as there being evidence of a lack of adverse effects at human-relevant exposures in laboratory studies, including those that provide positive evidence of adverse effects in animals exposed during perinatal life at exposure levels far in excess of those experienced by humans. "Minimal concern" was designated when data from studies in humans and animals are not sufficient to determine if BPA adversely affects reproduction. "Some concern" was assigned based on laboratory animal studies that provide "limited" evidence of adverse effects from low-level exposure but the evidence is not strong enough to indicate adverse effects in humans. NTP defined "concern" as implying that there is limited evidence for adverse effects at low doses in some animal studies, but that findings have not been replicated in other studies by independent investigators, there are questions on the suitability of various experimental approaches and/or the relevance of the specific animal models used for evaluating potential human risks, and/or there is an incomplete understanding or agreement on the potential adverse nature of reported effects. Finally, "serious concern" is designated when NTP determined there is at least "limited evidence" for adverse effects in humans at doses similar to human exposures (*e.g.*, in infants).

NTP concluded that there is "negligible concern" that exposure to BPA causes reproductive effects in non-occupationally exposed adults and that there is "minimal concern" for workers exposed to higher BPA levels in occupational settings (NTP, 2008a; NTP, 2008b). Consistent with this, JECFA (2010) concluded that there is considerable uncertainty as to whether BPA has any effect on conventional reproductive endpoints in rodents at doses below 1 mg/kg-day by the oral or subcutaneous route. EU (2003) classified BPA as a Category 3 reproductive toxicant. This category defines substances which cause concern for human fertility. It is based on sufficient evidence in animal studies to cause a strong suspicion of impaired fertility (irrespective of the relevance of dose levels to humans), but for which evidence is insufficient for categorization in Category 2 (substances that should be regarded as impairing human fertility). An EFSA (2010) Panel concluded that low-dose exposure to BPA poses no reproductive risk. The current perspective of US FDA (2012) is similar, with a conclusion of negligible concern for

reproductive effects of BPA at low doses. In addition, BPA is not listed as a chemical known to the state of California to cause reproductive toxicity under California's Proposition 65 (Cal EPA, 2012).

Although some reproductive effects have been reported in robust studies at high doses, there is no consistent evidence for effects at low doses. In addition, multiple governmental and regulatory bodies have concluded that BPA is not likely a reproductive toxicant at low doses. The lowest dose associated with reproductive effects in the robust studies is 500 mg/kg-day (Tyl *et al.* 2002), a dose that is at least six orders of magnitude higher than the estimates for current human exposures discussed above in Section 3.1. Thus, the evidence indicates that there is **low** concern for the reproductive toxicity of BPA at current human exposures.

3.2.4 Developmental Toxicity

No evidence for developmental toxicity has been observed in standard developmental toxicology studies of BPA in rats and mice. Although some recent low-dose studies using non-standard methods have reported conflicting results [*e.g.*, in mice, adverse effects on male prostate weight have been reported at dose levels in the range 2-50 µg/kg (Timms *et al.*, 2005; Welshons *et al.*, 1999)], these results have not been replicated in studies using more rigorous methods. One of two studies that did not replicate these results included additional dose levels and used larger group sizes compared to those used in either of the two studies that reported effects (Tyl *et al.*, 2008). Furthermore, no functional changes in reproductive parameters or reproductive organ development were observed in a recent rat two-generation study using similar dose levels (Ema *et al.*, 2001). In addition, several other robust studies have investigated the same reproductive and developmental endpoints as those examined by Tyl *et al.* (2008). These studies have been performed on a range of rat and mouse strains, at different life stages, over a wide array of doses, using a variety of exposure routes and durations, and have investigated a large assortment of endpoints (for a detailed review see Gray *et al.*, 2004; Goodman *et al.*, 2006; EFSA, 2006). Almost all of these studies have reported no effects or only small changes (unrelated to dose) in organ weight, tissue architecture, receptor expression, and hormone levels of unknown pathophysiological consequences. Overall, no consistent, reproducible, adverse effects have been observed.

Based on a five-point scale of possible levels of concern (*i.e.*, negligible concern, minimal concern, some concern, concern, and serious concern), NTP (2008a) concluded "some concern" for effects on the prostate gland in fetuses, infants, and children at current human exposures to BPA. As noted above, "some concern" is in the middle of a five-level qualitative scale that the NTP has defined and is designated when laboratory animal studies provide only "limited" evidence of adverse effects from low-level exposure. NTP has "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 BPA. As noted above, minimal concern implies that data from studies in humans are not sufficient to determine if BPA adversely affects development. The NTP has negligible concern (*i.e.*, there is no evidence) that exposures of pregnant women to low doses of BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring.

US FDA concluded that there were adequate margins of safety (*i.e.*, ratios of the lowest dose levels that cause adverse effects in experimental studies to human exposure levels) at current levels of BPA exposure from uses in food contact materials, and that the data on endpoints such as prostate effects and developmental toxicity were insufficient to alter the no observable adverse effect level (*i.e.*, the highest dose that produces no noticeable adverse effect), meaning that there is no indication of low-dose effects of BPA (US FDA, 2008). EFSA concluded that the available evidence does not raise concern regarding developmental toxicity of BPA at low (*i.e.*, < 5 mg/kg-day) doses (EFSA, 2010).

Although NTP concluded that there is "some concern" for developmental effects on the prostate, this is based on results from very few studies with methodological limitations, and this has not been shown in several robust studies evaluating such effects. In addition, other governmental and regulatory bodies did not conclude that BPA is a developmental toxicant at low doses. Together, the evidence indicates that there is **low** concern for the developmental toxicity of BPA at current human exposures.

3.2.5 Endocrine Disruption

An endocrine disruptor interferes with the action of hormones in a living organism; however, the classification of a chemical as an endocrine disruptor does not necessarily mean that it will cause harm at any exposure. Studies have shown that BPA has estrogen-like, or endocrine, activity, meaning it can mimic or alter the effects of the body's natural hormones. While toxicity tests used to develop safety guidelines for BPA found that the lowest dose at which adverse effects in animals were observed was 50 mg/kg-day, several orders of magnitude higher than human exposures, hormonal effects were only found at much higher doses (Ashby and Odum, 2004).

EU (2003) classified BPA as a Category 1 endocrine disruptor (defined as having evidence of endocrine disrupting activity in at least one species using intact animals), but this classification does not consider dose. NTP concluded that there was insufficient evidence for endocrine-mediated effects of BPA at low doses and that there is no biologically plausible explanation for effects that appear at low doses but not higher doses (NTP, 2008a).

Together, the evidence indicates that there is **low** concern for the endocrine disrupting activity of BPA at current human exposures.

3.2.6 Neurotoxicity

Several investigators examined whether low doses of BPA during fetal development can affect subsequent behavior of pups. Early studies evaluated a number of endpoints, but their interpretation is hampered by a lack of understanding of whether results are applicable to humans. Even so, there is no consistent evidence among these studies that low doses of BPA cause adverse effects on behavioral endpoints (*e.g.*, Ema *et al.*, 2001; Palanza *et al.*, 2002; Aloisi *et al.*, 2002). Based on this limited database, NTP (2008a) stated it had "some concern" for effects on the brain and behavior. As stated previously, "some concern" is in the middle of a five-level scale that the NTP has defined, and it reflects the fact that the scientists who have examined the human and animal data recognize that these studies may not be relevant to humans.

In November 2010, WHO and the United Nations FAO, with the support of EFSA, Health Canada, the US National Institute for Environmental Health Sciences, and US FDA, convened a panel of over 30 international experts to review toxicological and health aspects of BPA (JECFA, 2010). The panel concluded, "[S]ome emerging new end-points [including neurodevelopment] in a few studies show associations at lower levels...There is considerable uncertainty regarding the validity and relevance of these" (JECFA, 2010). Since this publication, two recent studies were conducted (one by US EPA) using robust, validated methodologies to assess the effects of low doses of BPA on the developing brain. These studies found no evidence of neurological effects in animals exposed to low doses of BPA (Stump *et al.*, 2010; Ryan *et al.*, 2010). EFSA (2010) concluded that that the currently available data are not sufficient to indicate neurobehavioral toxicity as an endpoint of concern for BPA.

Because the most robust studies of the potential neurotoxicity of BPA indicate a lack of neurodevelopmental effects at relevant human exposures, the evidence indicates that there is **low** concern for the neurotoxicity of BPA at current human exposures.

3.2.7 Immune System Toxicity

Currently, the data are insufficient for drawing conclusions about possible immunological effects from low-dose BPA exposure to humans. The multi-generational studies of BPA performed in rodents have reported no pathologies that would indicate adverse immunological effects (Tyl *et al.*, 2002, 2008; Ema *et al.*, 2001). WHO stated that there is no clear evidence that BPA interferes with immune function (JECFA, 2010). The EU (2003) risk assessment concluded that studies of mice exposed to ultraviolet light and BPA suggest that BPA can induce a photosensitizing reaction that appears to be mediated by the immune system, but the test methods employed were not fully validated.

Together, the evidence indicates that there is **low** concern for the immunotoxicity of BPA.

3.2.8 Acute Toxicity

In general, BPA has low acute toxicity by all routes of exposure relevant to human health (EU, 2003). LD_{50} (the lethal dose for 50% of the population tested) values in rats and mice are above 2,000 mg/kg (EU, 2003). Together, the evidence indicates that there is **low** concern for the acute toxicity of low doses of BPA.

3.2.9 Systemic/Organ Toxicity

There is no evidence for systemic toxicity of BPA at low doses. Most of the BPA to which humans are exposed is ingested orally and metabolized in the liver and intestine, then eliminated in urine, so it never reaches the general circulation nor accumulates in the body after ingestion (Völkel *et al.*, 2002, 2005). Because of this, there is **low** concern for systemic/organ toxicity of BPA at low doses.

3.2.10 Skin Sensitization

There is no evidence to suggest that BPA causes skin sensitization at low doses. Studies concerning skin sensitization consist of case reports that are confounded by co-exposure to other chemicals. Limited human anecdotal information of uncertain reliability is available from written industry correspondence suggesting that workers handling BPA have, in the past, experienced skin irritation. It cannot be determined whether the reported skin reactions were related to skin sensitization or irritation (EU, 2003, 2008). Recent studies confirm that there are no skin effects from workers observed during routine one-to-three year medical examinations (EU, 2003, 2008).

Together, the evidence indicates that there is **low** concern for the skin sensitization of BPA.

3.2.11 Respiratory Irritation/Sensitization

The concentration of BPA in consumer products such as paint and varnish is estimated at < 0.0004% BPA. At these concentrations, EU (2008) concluded that there is no concern that the irritating properties of BPA will be expressed and therefore there are no concerns for BPA as a respiratory irritant. There are no data from which to evaluate the potential for BPA to be a respiratory sensitizer (EU, 2003, 2008).

Together, the evidence indicates that there is **low** concern for the respiratory irritation/sensitization of BPA.

3.2.12 Skin Irritation/Corrosion

There is no evidence to suggest that BPA causes skin irritation or corrosion at low doses. Recent studies do not confirm any skin sensitization at concentrations up to 30% BPA, and medical surveillance reports from five BPA manufacturing plants also did not identify any workers who had self-reported skin effects or skin issues observed during routine one- to three-year medical examinations (EU, 2003). Moreover, the EU risk assessment concluded that BPA exposure results in "negligible" skin irritation (EU, 2003). Together, the evidence indicates that there is **low** concern for skin irritation/corrosion of BPA.

3.2.13 Eye Irritation/Corrosion

No dose-response information is available on BPA as an eye irritant (EU, 2003). Limited, anecdotal human evidence suggests that eye irritation can occur following occupational exposure to BPA, but it is unlikely to occur if good occupational hygiene practices are in operation. The EU (2003) risk assessment concluded that BPA has the potential to cause "serious damage" to the eyes, but this is based on studies of rabbits that received direct instillation of high doses of BPA into the eye. Together, the evidence indicates that there is **low** concern for eye irritation/corrosion of BPA at current human exposures.

3.3 Ecological Effect Assessment

Most environmental releases of BPA occur during the manufacture of BPA-containing products, when residual BPA in wastewater is released from treatment plants into receiving streams (Cousins *et al.*, 2002; Flint *et al.*, 2012; Staples *et al.*, 2011). BPA's half-life in soil and water is on the order of 4.5 days, while in air it is less than one day (Cousins *et al.*, 2002; Flint *et al.*, 2012). BPA has a low bioconcentration factor and is rapidly metabolized in fish, with a half-life of less than one day (Cousins *et al.*, 2002; Flint *et al.*, 2012). Studies indicate that adverse effects on aquatic ecosystems at low levels of BPA exposure are not expected (Staples *et al.*, 2002).

3.3.1 Acute Aquatic

The survival of aquatic species exposed to BPA in 48- or 96-hour test systems has been evaluated in a number of fish and invertebrates (Staples *et al.*, 2002). The LC_{50} (the lethal concentration for 50% of the population tested) values for these tests range from 4,600 to 17,930 µg/L in fish and 960 to 10,000 µg/L in invertebrates. These data indicate that there is **moderate** concern for the acute aquatic toxicity of BPA.

3.3.2 Chronic Aquatic

Growth and development are critical to a species' ability to reproduce. Staples *et al.* (2002) summarized multiple studies that evaluated BPA's effects on these parameters. Eight studies evaluating different species of fish and an amphibian species for durations of 28 to 431 days found the lowest BPA concentrations that caused effects ranged from 1,820 to 11,000 µg/L. No observed effect concentrations (NOECs) in these studies ranged from 120 to 3,640 µg/L. More recently, Staples *et al.* (2011) reported a NOEC range of 16 to 1,280 µg/L for fathead minnows. According to the EU (2003) risk assessment, the NOECs of BPA for growth rate in fish range from 640 to 3,640 µg/L. In aquatic invertebrates studies, growth effects were observed in a copepod, with an effect concentration for 10% of the population tested

(EC_{10}) of 100 µg/L (Andersen *et al.*, 2001) but Staples *et al.* (2002) concluded that this study is not valid for use in hazard assessment, as few methodological details or results are reported. In a different aquatic invertebrate (*Daphnia magna*), no effects on molting were observed at concentrations up to 3,160 µg/L (the highest tested). In algae, growth effects were reported for freshwater green algae (EC_{10} of 1,360 to 1,680 µg/L) and the marine diatom (EC_{10} of 400 to 690 µg/L). These data indicate that there is **moderate** concern for the chronic aquatic toxicity of BPA.

3.4 Environmental Fate Assessment

The environmental hazards of persistence (*i.e.*, slow to degrade) and bioaccumulation (*i.e.*, collection in animal tissues or organs) have an additional level of concern of "very high." The threshold values for these hazards in the Green Screen were set to be highly protective of human health and the environment (Rossi and Heine, 2007).

3.4.1 Persistence

BPA has low volatility and a short half-life in the atmosphere, is rapidly biodegraded in water, and is not expected to be stable, mobile, or bioavailable from soils (Cousins *et al.*, 2002; EU, 2003, 2008). Because BPA is readily biodegradable, there is **low** concern for the persistence of BPA in the environment.

3.4.2 Bioaccumulation

The bioaccumulation factor for BPA in fish is 67 (EU, 2003) and the bioconcentration factor in fish ranges from less than 20 to 68 (Flint *et al.*, 2012); thus, there is **low** concern for the bioaccumulation of BPA.

3.5 Physical/Chemical Properties

Threshold values for flammability and explosivity are set in the Green Screen because these properties lend them to be particularly hazardous to workers and communities (Rossi and Heine, 2007).

3.5.1 Explosivity

The minimum explosive concentration for BPA in air is 0.012 g/L with >5% oxygen (EU, 2008), and BPA dust is flammable if ignited (US EPA, 2012b). There is **moderate** concern for the explosivity of BPA.

3.5.2 Flammability

The flash point of BPA ranges from 22.7 C to 79.4 C (EU, 2008), so BPA falls within the Globally Harmonized System of Classification and Labelling of Chemicals Categories 3 and 4 for flammability (UN, 2011). There is **moderate** concern for the flammability of BPA.

3.6 Conclusions for Levels of Concern

The hazard-based thresholds for the determination of the levels of concern for each effect category are listed in Table 3. We determined which thresholds were met for each category, based on hazard, and these are indicated in bold font in Table 3. For categories that were above a low level of concern based on hazard, we incorporated information on exposure to determine a risk-based level of concern, indicated in the last column of Table 3.

Table 3 Hazard Thresholds and Determinations of Risk-based Levels of Concern for Effect Categories

Hazard	Very High (VH)	High (H)	Moderate (M)	Low (L)	Risk-based Level of Concern
Human Health					
Carcinogenicity		Human evidence; WoE demonstrates potential for human effects; NTP known/reasonably anticipated; OSHA carcinogen; US EPA probable; CA Prop 65; IARC Group 1 or 2A; EU Category 1 or 2; or GHS Category 1A or 1B	Suggestive animal studies; Analog data; Chemical class known toxicity; US EPA possible; IARC Group 2B; EU Category 3; or GHS Category 2	**No basis for concern identified**; or IARC Group 3 or 4	Low
Mutagenicity/ Genotoxicity		Human evidence; WoE demonstrates potential for human effects; EU Category 1 or 2; or GHS Category 1A or 1B	Suggestive animal studies; Analog data; Chemical class known toxicity; EU Category 3; or GHS Category 2	**No basis for concern identified**	Low
Reproductive Toxicity		Human evidence; WoE demonstrates potential for human effects; NTP CERHR/OHAT; CA Prop 65; EU Category 1 or 2; or GHS Category 1A or 1B	**Suggestive animal studies**; Analog data; Chemical class known toxicity; **EU Category 3**; or GHS Category 2	No basis for concern identified	Low
Developmental Toxicity		Human evidence; WoE demonstrates potential for human effects; **NTP CERHR/OHAT**; or CA Prop 65	Suggestive animal studies; Analog data; or Chemical class known toxicity	No basis for concern identified	Low

Hazard	Very High (VH)	High (H)	Moderate (M)	Low (L)	Risk-based Level of Concern
Endocrine Disruption		Human evidence; or WoE demonstrates potential for human effects	**Suggestive animal studies;** Analog data; Chemical class known toxicity; **EU Category 1 or 2**; or Japanese list	No basis for concern identified	Low
Neurotoxicity		Human evidence; or WoE demonstrates potential for human effects	**Suggestive animal studies;** Analog data; or Chemical class known toxicity	No basis for concern identified	Low
Acute Toxicity		LD_{50} < 50 mg/kg (oral); LD_{50} < 200 mg/kg (dermal); LC_{50} < 500 ppm (gas); LC_{50} < 2 mg/L (vapor); LC_{50} < 0.5 mg/L (dust/mist); US EPA Extremely Hazardous Substance List; or GHS Category 1 or 2	LD_{50} 50-2000 mg/kg (oral); LD_{50} 200-2000 mg/kg (dermal); LC_{50} 500-5000 ppm (gas); LC_{50} 2-20 mg/L (vapor); LC_{50} 0.5-5 mg/L (dust/mist); or GHS Category 3 or 4	**No basis for concern identified**	Low
Corrosion/ Irritation of Skin or Eye		Evidence of reversible effects in human population studies; WoE of irreversible effects in animal studies; or GHS Category 1 (skin or eye)	**Evidence of reversible effects in humans or animals;** GHS Category 2 or 3 – Skin Irritation; or GHS Category 2A or 2B – eye	No basis for concern identified	Low
Sensitization of Skin or Respiratory System		Human evidence; WoE demonstrates potential for human effects; GHS Category 1 (skin or respiratory); or Repeat responses in human skin patch tests	Suggestive animal studies; Analog data; or Chemical class known toxicity	**No basis for concern identified**	Low
Immune System Effects		Human evidence; or WoE demonstrates potential for human effects	Suggestive animal studies; Analog data; or Chemical class known toxicity	**No basis for concern identified**	Low

Hazard	Very High (VH)	High (H)	Moderate (M)	Low (L)	Risk-based Level of Concern
Systemic/Organ Toxicity		Human evidence; WoE demonstrates potential for human effects; GHS Category 1 – organ/systemic toxicity from single or repeated exposure	Suggestive animal studies; Analog data; Chemical class known toxicity; GHS Category 2 or 3 single exposure; or Category 2 repeated exposure	**No basis for concern identified**	Low
Ecotoxicity					
Acute Aquatic Toxicity		$LC_{50}/EC_{50}/IC_{50}$ < 1 mg/L; or GSH Category 1	**$LC_{50}/EC_{50}/IC_{50}$ 1-100 mg/L**; or GSH Category 2 or 3	$LC_{50}/EC_{50}/IC_{50}$ > 100 mg/L	Moderate
Chronic Aquatic Toxicity		NOEC < 0.1 mg/L; or GHS Category 1	**NOEC 0.1-10 mg/L**; or GHS Category 2, 3, or 4	NOEC > 10 mg/L	Moderate
Environmental Fate					
Persistence	Soil/sediment > 180 d; or Water > 60 d	Soil/sediment >160 to 180 d; Water >40 to 60 d; or Potential for long-range transport	Soil/sediment 30-60 d; or Water 7-40 d	Soil/sediment <30 d; Water <7 d; or **Readily biodegradable**	Low
Bioaccumulation Potential	BCF/BAF > 5000; or Absent such data, $logK_{ow}$ > 5	BCF/BAF > 1000-5000; Absent such data, log K_{ow} > 4.5-5; or WoE demonstrates bioaccumulation in humans or wildlife	BCF/BAF 500-1000; Absent such data, log K_{ow} 4-4.5; or Suggestive evidence of bioaccumulation in humans or wildlife	**BCF/BAF < 500**; or Absent such data, log K_{ow} < 4	Low
Physical/Chemical Properties					
Explosive		GHS Category: Unstable explosives or Divisions 1.1, 1.2, or 1.3	**GHS Category: Divisions 1.4 or 1.5**	No basis for concern identified	Moderate
Flammable		GHS Category 1 – Flammable gases; GHS Category 1 – Flammable aerosols; or GHS Category 1 or 2 – Flammable liquids	GHS Category 2 – Flammable gases; GHS Category 2 – Flammable aerosols; or **GHS Category 3 or 4 – Flammable liquids**	No basis for concern identified	Moderate

Abbreviations: BAF = bioaccumulation factor; BCF = bioconcentration factor; EC_{50} = median effect concentration; EU = European Union; GHS = Globally Harmonized System of Classification and Labeling of Chemicals; IARC = International Agency for Research on Cancer; IC_{50} = mean inhibitory concentration; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; $logK_{ow}$ = log-octanol water partition coefficient; NOEC = no observed effect concentration; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.

4 Determination of Benchmark Criteria

Using the benchmark criteria in Table 2, we determined the Green Screen benchmark level for BPA based on our analysis in Section 3, and have listed the reasons for this determination in Table 4. BPA passes all the criteria for Benchmark 1, as it has low human toxicity across all categories, moderate ecotoxicity, and low persistence and bioaccumulation. BPA also passes the criteria for Benchmark 2 and 3 for these reasons; in addition, BPA has moderate explosivity and flammability. BPA does not pass the Benchmark 4 criteria, however, because of the moderate ecotoxicity concerns.

Table 4 Green Screen Benchmark Determination

Reasons for Benchmark	Benchmark Achieved/Stopped By
Moderate acute and chronic ecotoxicity Moderate explosivity and flammability Low human toxicity Low bioaccumulation and persistence	Benchmark 3/Stopped by moderate ecotoxicity

In the Green Screen, the Benchmark 3 criteria are designed for chemicals that are "on the cusp of being highly benign: they have some hazard characteristics of modest concern, but no characteristics of high concern" (Rossi and Heine, 2007). We have modified this to indicate that Benchmark 3 chemicals have some *risk* characteristics of modest concern (in the case of BPA, this is only for ecotoxicity effects) and no characteristics of high concern. According to Rossi and Heine (2007), the designation of a Benchmark 3 chemical is interpreted as meaning that the chemical may still be used in consumer products and materials, but there is "still opportunity for improvement," in terms of replacement of the chemical with one for which toxicity is reduced to the lowest possible level while achieving the desired performance and function (*i.e.*, a "safer" chemical). In the case of BPA, a safer chemical would have a lower level of concern regarding ecotoxicity, based on the Green Screen thresholds for the categories of acute and chronic aquatic toxicity, but not human toxicity, for which the risk-based level of concern is low.

5 Conclusions

We conducted a modified Green Screen evaluation of BPA that focused on assessing risks rather than hazards alone. When exposure was considered, we determined that BPA is of low concern for all human health and environmental effect categories assessed and of moderate concern for the ecotoxicity and physical/chemical property categories assessed in our evaluation. We determined that BPA passes the criteria for Green Screen Benchmark 3 ("use, but still opportunity for improvement"). The criteria for this benchmark are designed for chemicals that are "on the cusp of being highly benign" and that have some risk characteristics of modest concern and no characteristics of high concern. The designation of a Benchmark 3 chemical indicates that the chemical may still be used in consumer products and materials, but there is opportunity for improvement in terms of replacing the chemical with a "safer" one that has lower ecotoxicity compared to BPA.

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