

Response to Comments on the Draft Alternatives Assessment for Bisphenol A in Thermal Paper – January 2014

On July 31, 2012, the U.S. Environmental Protection Agency (EPA)'s Design for the Environment (DfE) program issued a draft alternatives assessment report titled *Bisphenol A (BPA) Alternatives in Thermal Paper*. Under its enhanced chemicals management program, EPA issued an action plan in March 2010 for BPA, including its use in thermal paper. The action plan called for the development of a multi-stakeholder alternatives assessment for BPA in thermal paper conducted by DfE. Thermal paper is widely used for cash register receipts, airline tickets, event and cinema tickets, and grocery store adhesive labels. This alternatives assessment evaluates the potential hazards associated with BPA and its functional alternatives. The draft report of this alternatives assessment was posted on the DfE website for public review and a 60-day comment period.

DfE's Alternatives Assessment Program helps industries choose safer chemicals and provides a basis for informed decision making by developing a detailed comparison of potential human health and environmental effects of chemical alternatives. More information on the DfE Alternatives Assessment Program is available on the DfE website at http://www.epa.gov/dfe/alternative_assessments.html.

DfE received six sets of formal written comments on the draft report *Bisphenol A (BPA) Alternatives in Thermal Paper* during the comment period, which was July 31 to October 1, 2012. In addition, DfE staff had telephone and in-person conversations with stakeholders during the comment period to discuss the report. The comments submitted convey the viewpoints of variety of interests including those of chemical manufacturers, thermal paper manufacturers, non-governmental organizations, and trade associations. Of the comments DfE received, most addressed the hazard profiles of specific chemicals. DfE greatly appreciates the effort of the commenters, including those who shared their input less formally. This document addresses all formal and informal comments that collectively improve the scientific basis and utility of the alternatives assessment.

Below, DfE presents and discusses the comments received on the draft alternatives assessment and, where appropriate, indicates changes made to the final text of *Bisphenol A (BPA) Alternatives in Thermal Paper*. DfE has also made minor editorial and non-substantive technical corrections to the report. DfE received comments on 1) the hazard evaluation of BPA and its alternatives, which are addressed first in this document, and 2) general report content. Please note that the comments have been paraphrased, summarized, and combined, as appropriate, for brevity and clarity; full versions, as well as the final alternatives assessment report, are available on the DfE website at <http://www.epa.gov/dfe/pubs/projects/bpa/about.htm>.

Comments and DfE Responses

I. Comments on the Hazard Evaluation of BPA and its Alternatives

Summary Table Presentation

Comment: Table 4-4 color gradations suggest ranking. A different background color should be used in the table, as readers may think that colors represent chemical similarity or comparative hazard.

Response: The use of colors in Table 4-4 was intended to designate chemicals that share structural similarities. To avoid potential confusion, DfE has eliminated the color gradations in Table 4-4 and has added descriptions of the structural similarities of each chemical grouping.

Data Gaps and Estimated Data

Comment: The assessment relies heavily on calculated values versus experimental values. Ecological Structure-Activity Relationship (ECOSAR) model calculations should only be used in the form of a weight-of-evidence approach in combination with other endpoint information. The stand-alone use of ECOSAR should be avoided because of a low reliability of the estimated toxicity values.

Response: As indicated in the report, estimated values derived from ECOSAR models were used to assign hazard designations for aquatic toxicity endpoints in the absence of sufficient experimental data. Methodology for using ECOSAR estimates in the absence of experimental data is discussed in detail in Chapter 4 of the document.

EPA appreciates concerns about overreliance on predictive methods in chemical assessment, and problems this may cause. In particular, EPA understands and applies the OECD principles relating to proper use of QSARs (the so-called Setubal Principles), such as the need to apply SARs only within their domain of applicability. On the other hand, the realities of chemical assessment in a data-poor environment are such that compromises that can be avoided in an ideal world are often unavoidable in the one we actually inhabit. In responding to this situation, EPA certainly does make every attempt reasonably possible to use first measured toxicity and other data, and only then after appropriate quality assurance. But in the frequent situation where predictive methods must then be applied, tools that are well established are given preference. ECOSAR and EPI Suite are such tools and have been thoroughly vetted in scientific and regulatory arenas over many years and in numerous publications in peer-reviewed sources. More information on the use of ECOSAR is available at: <http://www.epa.gov/oppt/newchems/tools/21ecosar.htm>.

Comment: There are many data gaps for the chemicals being assessed for all of the various health endpoints. There needs to be more research done on the potential adverse health effects of the 19 chemicals being assessed before any are used in thermal cash receipts or we may be replacing one hazardous substance for another.

Response: DfE acknowledges this comment and agrees that additional experimental data would be advantageous to the DfE Alternatives Assessment process. The report contains the best information that is available in the literature and that can be modeled. Decision making based on the data in the report is a significant improvement over decision making in the absence of that information. No change to the report is required.

Comment: EPA should rank or bin chemicals by level of concern and highlight data gaps. The assessment currently offers little tangible guidance to manufacturers seeking safer developers and obscures an important finding that many alternatives pose similar risks to BPA in thermal papers. Every chemical alternative to BPA was found to pose “High” or “Very High” hazard in at least one health or environmental endpoint.

Response: DfE does not rank chemicals. DfE Alternatives Assessments are intended to provide the best information from testing and modeling to support decision making by the stakeholder community. DfE recognizes that significant tradeoffs may exist. The weighting and ranking of chemicals require context and subjectivity, which is best left to the users of the information provided in the alternatives assessment. DfE does not plan to choose or impose a decision-making scheme. Organizations such as Clean Production Action have developed chemical scoring methodologies in partnership with industry sectors. Such methodologies may be used with the information from DfE Alternatives Assessments as a decision-making tool. No change to the report is required.

Aquatic Toxicity

Comment: Growth rate is more common instead of biomass to evaluate toxicity to algae. According to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals, “The preferred observational endpoint in this study is algal growth rate inhibition because it is not dependent on the test design, whereas a biomass study depends both on growth rate of the species as well as the test duration and other elements of test design.”

Response: As described in Chapter 4, the hazard designation for aquatic toxicity is generally based on the study results associated with the most sensitive effect of the most sensitive species. All available data for the aquatic toxicity endpoints were considered, including both algal growth rate and biomass effects in algae when available. However, for the purposes of assigning hazard designations, the most sensitive effect was used.

Endocrine Activity

Comment: Three comments were submitted regarding the rationale for the approach taken on endocrine activity in the report and the feedback received during the expert review process. Specific points include:

- It is disappointing that endocrine activity is not recognized in the report as an adverse health effect or endpoint in Table 4-4. The report inconsistently refers to endocrine disruption as an endpoint or a human health hazard (Section 6.1.1). Endocrine disruption is viewed as a human health hazard in the 2009 Endocrine Society Review.

- There is a lack of analysis of the threat of hormone disruption. Its absence from Table 4-4 creates the impression that hormone disruption is not a top concern for alternatives to BPA in thermal paper. Many of the potential replacements for BPA are molecules with a phenolic structure similar to BPA and are suspected to have similar toxicological risks. Given that the DfE Alternatives Assessment program was prompted by BPA's hormone-disrupting properties and widespread human exposure, this endpoint must be a high priority in assessing the alternatives and must be reflected clearly in the Agency's summary and conclusions.
- The hazard summaries indicate that data on hormone disruption are available for BPA and 11 of 19 replacement chemicals. Nine of 11 chemicals with available test data have been shown to interfere with hormone systems in at least one study. The remaining nine alternatives have not been tested, and their ability to stimulate or inhibit responses of thyroid or sex hormones remains uncharacterized. There is sufficient evidence to flag the nine tested chemicals for "potential endocrine activity" in Table 4-4.

Response: As described in the DfE Alternatives Assessment Criteria,¹ which went through a public comment period, evidence for endocrine activity is described in a summary statement; DfE does not assign High, Moderate, or Low hazard designations for endocrine activity. This is an appropriate approach because there is not a consensus on what constitutes High, Moderate, or Low concern for endocrine activity. The summary of endocrine activity relies on representative studies and expert panel review reports. During the report's internal peer review process, DfE solicited input from the EPA Endocrine Disruptor Screening Program and made adjustments to its data summaries to address the program's comments, including clarification that the review was not intended to be comprehensive. DfE also received feedback from National Institute of Environmental Health Sciences (NIEHS)/National Toxicity Program (NTP) and incorporated its suggestions to include additional data on endocrine activity.

Comment: When asked in November 2011 why endocrine disruption was not listed in the hazard summary table, EPA stated that there were not enough studies that showed endocrine disruption caused adverse health effects. However, the draft report lists an ample number of studies on endocrine disruption for several of the reviewed chemicals.

Response: There are several reasons why DfE does not include endocrine activity in the hazard summary table. First, the data for endocrine activity are scarce. Although studies have been conducted for many chemicals in this report, the studies are mostly limited to *in vitro* assays measuring receptor binding. This type of study is insufficiently informative as to the level or degree of hazard associated with perturbations detected in *in vitro* assays. EPA acknowledges there is at this time a lack of consensus on the number and types of studies that are needed to draw such conclusions. Second, DfE Alternatives Assessment Criteria for hazard evaluation are based on consensus criteria, such as the Globally Harmonized System (GHS) for Classification and Labelling. There is a lack of consensus on the development of criteria for assessing endocrine activity, and DfE will not independently establish criteria.

¹ http://www.epa.gov/oppt/dfe/alternatives_assessment_criteria_for_hazard_eval.pdf

Comment: There are many data gaps in the report. Data on endocrine activity are available for BPA and for 10 of the 19 alternatives included in the report. For chemicals without available data on endocrine activity, this was acknowledged with a “no data available” entry.

Response: DfE acknowledges the comment and notes that the hazard profiles include a similar statement (“no data located”). No change to the report is required.

Comments on Specific Hazard Evaluations

BPA - General

Comment: Three comments were submitted regarding the use of the latest data in the BPA hazard profile. Specific points include:

- The updated Japanese Risk Assessment should be included in the risk assessment section on page 4-33 of the draft alternatives assessment report.
- The recent studies conducted by the U.S. Food and Drug Administration (FDA) should be included with a recent physiologically based pharmacokinetic (PBPK) model study in the absorption, distribution, metabolism, and excretion (ADME) hazard profile section.
- New data should be incorporated into the hazard profile. EPA’s failure to include significant studies that were readily available when the draft report was released is further evidence that EPA is not relying on “the best information available” and has not “reviewed the open literature” as stated in EPA’s alternatives assessment criteria document.

Response: The strategy for evaluating BPA based on the National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) (2008) and the Food and Agriculture Organization/World Health Organization (FAO/WHO) (2011) expert panel review reports was determined prior to initiating the review and the stakeholders were fully briefed regarding this approach. This strategy was necessary because over a hundred new studies have been published since publication of the NTP and WHO reports. If the published data result in updates to the values in the NTP-CERHR (2008) or FAO/WHO (2011) expert panel review reports that were used in BPA’s hazard profile, DfE will modify the hazard designations accordingly.

Carcinogenicity of BPA

Comment: The BPA Action Plan states “Given that human exposures from Toxic Substances Control Act (TSCA) uses of BPA are minor compared with human exposures from uses under FDA jurisdiction, EPA considers that FDA has the lead in making human health judgments on BPA.” EPA should follow FDA’s lead and assign a Low carcinogenicity hazard designation for BPA.

Response: FDA has clearly stated that it supports the conclusions of the NTP-CERHR (2008) evaluation, which is the basis for DfE’s hazard evaluation. Specifically, FDA states “Studies employing standardized toxicity tests have thus far supported the safety of current low levels of human exposure to BPA. However, on the basis of results from recent studies using novel

approaches to test for subtle effects, both NTP and FDA have some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children.”² The NTP-CERHR (2008) report does not rule out the potential carcinogenicity of BPA. Moreover, based on the DfE criteria for this endpoint, there are multiple lines of evidence that justify the Moderate hazard designation, including the appearance of precancerous lesions in some animal models and the presence of a structural alert for carcinogenicity.

Comment: OncoLogic data for carcinogenicity in the BPA hazard profile should be removed because high-quality measured data are offered (i.e., NTP 2-year studies; Keri, Ho et al. 2007; FAO/WHO 2011).

Response: OncoLogic results represent a line of evidence that can be compared to the experimental results for structurally similar chemicals. The comparison of model results to measured data – including standard and nonstandard bioassay results can help stakeholders evaluate the robustness of data for a given chemical class or set of functional groups. As noted in the response to other stakeholder comments below, OncoLogic correctly identified a structural alert for phenolic compounds. No change to the report is required.

Comment: The BPA hazard profile does not provide the necessary “evidence of carcinogenicity” to support a Moderate hazard designation because the results of both NTP 2-year studies in rats and mice provide no convincing evidence of a carcinogenic effect for BPA. Both studies were designated as “adequate” for data quality. These studies provide the best available data for assigning a carcinogenicity hazard designation for BPA. According to EPA’s hazard evaluation criteria document, the results of these studies support a Low hazard designation.

Response: The DfE definition of Moderate concern as discussed in the methodology section of Chapter 4 is based on the International Agency for Research on Cancer’s (IARC’s) definition for limited evidence of carcinogenicity in animals: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs. (For more information, please see the Preamble to the IARC Monographs at <http://monographs.iarc.fr/ENG/Preamble/index.php>.) The evidence for Moderate concern for carcinogenicity includes: unresolved questions regarding the adequacy of standard bioassay data due to missing early life exposures (b), and indication of preneoplastic lesions (c). DfE concluded that cancer risk cannot be ruled out at this time.

Comment: Five comments were submitted regarding carcinogenicity bioassays, endocrine activity, and expert judgment. Specific points include:

- The BPA hazard profile does not provide the necessary “evidence of carcinogenicity” to support a Moderate hazard designation because no studies are cited that provide “evidence of carcinogenicity” as defined for the term “carcinogenic.” The FAO/WHO

² <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm197739.htm#studies>

(2011) review clearly concludes that “there is currently insufficient evidence on which to judge the carcinogenic potential of BPA.”

- The BPA hazard profile does not provide the necessary “evidence of carcinogenicity” to support a Moderate hazard designation because the 2007 review by Keri et al. does not support a Moderate hazard designation. The conclusions from this review indicate that the authors are confident of endocrine activity and the estrogenic properties of BPA, and the carcinogenic properties of estradiol-17 β . None of these conclusions provide evidence of carcinogenicity for BPA.
- The carcinogenicity summary paragraph in the BPA hazard profile refers to “concern for carcinogenicity” and “uncertainty.” EPA’s hazard criteria document provides no basis to use “concern” or “uncertainty” to assign a hazard designation.
- The carcinogenicity summary paragraph in the BPA hazard profile asserts that “carcinogenicity cannot be ruled out at this time.” The criterion for carcinogenicity designations does not require that carcinogenicity be ruled out. Rather it requires evidence for carcinogenicity, meaning that carcinogenicity must be ruled in, not out.
- EPA’s carcinogenicity designation for BPA is inconsistent with numerous agencies worldwide that have comprehensively reviewed the scientific evidence and found that BPA is not a carcinogenic hazard or risk, which clearly supports a Low hazard designation.

Response: DfE states in the hazard evaluation that BPA has been tested in standard carcinogenicity bioassays and it is generally agreed that it is not a direct-acting carcinogen. However, there is concern that the endocrine activity associated with BPA increases cancer risk. FAO/WHO (2011) and NTP-CERHR (2008) raise this concern based on a number of academic studies that demonstrate potential associations with increased risk of breast and prostate cancer. This potential is reflected through OncoLogic’s structural alert for phenolic compounds that exhibit endocrine activity. Additionally, NTP, in conjunction with FDA, is re-running the cancer bioassay for BPA with modifications that include *in utero* and early life exposures to investigate this concern. Based on NTP-CERHR (2008), FAO/WHO (2011), and EPA’s analyses, DfE assigned a Moderate hazard designation for carcinogenicity for BPA.

In the absence of definitive, negative experimental results for this endpoint, DfE Alternatives Assessment methodology (as discussed in Chapter 4) requires the assignment of a Moderate designation.

Reproductive Toxicity of BPA

Comment: Five comments were submitted regarding the evidence used for the reproductive toxicity hazard designation assigned for BPA. Specific points include:

- Reproductive toxicity for BPA should be changed from High to Moderate. The no observed adverse effect levels (NOAELs) cited in the EPA hazard summary are derived from a three-generation reproduction study in rats reported by Tyl et al. (2002) as ppm of BPA in the diet. NTP-CERHR reported the value as 47.5 mg/kg bw-day. NTP-CERHR (2008) nor EPA provides an explanation of how they were derived, or any basis to justify why these values should override the values derived in the study itself. For male

reproductive toxicity, the authors reported a NOAEL of 750 ppm (~50 mg/kg bw-day), not 75 ppm (~5 or 4.75 mg/kg bw-day) as indicated in the EPA hazard summary.

- Various regulatory agencies that have reviewed the Tyl et al. (2002) study in detail have all accepted the 50 mg/kg bw-day NOAEL for male reproductive toxicity (i.e., European Food Safety Authority, EU risk assessment, and Japanese risk assessment). The reproductive toxicity summary and hazard profile should be corrected to show NOAELs for male and female reproductive toxicity of 50 mg/kg bw-day. Based on EPA's hazard identification criteria document, these values justify at most a Moderate hazard designation. Since lowest observed adverse effect levels (LOAELs) and NOAELs are both considered, this value might also support a Low hazard designation since the LOAEL that corresponds to the 50 mg/kg bw-day NOAEL falls in the Low hazard designation according to EPA's hazard evaluation criteria document.
- The NTP-CERHR (2008) expert panel calculated benchmark dose (BMD) values for the various endpoints in the Tyl et al. (2002) study. For the preputial separation (PPS) endpoint (F1, F2 and F3 generations), the various BMD values range from 163 to 547 mg/kg bw-day. As noted in EPA's hazard evaluation criteria document, "When available and appropriate, the results of benchmark dose modeling will also be considered." The BMD values calculated by the NTP-CERHR (2008) expert panel would support at most a Moderate hazard designation for reproductive toxicity. Regardless of whether NOAEL, LOAEL, or BMD values are used, the weight of evidence supports a reproductive toxicity hazard designation that is no higher than Moderate.
- Parental systemic toxicity was observed in rats at both 7,500 ppm (500 mg/kg/day) and 750 ppm (50 mg/kg/day), so the parental systemic toxicity NOAEL was 75 ppm (5 mg/kg/day). In mice, parental systemic toxicity was observed at both 3,500 ppm (600 mg/kg/day) and 300 ppm (50 mg/kg/day) so the parental systemic toxicity NOAEL was 30 ppm in mice (also 5 mg/kg/day). The dietary concentrations were set in ppm to provide comparable intakes of BPA in mg/kg/day for both species. This means that the reproductive/postnatal NOAEL was at least 50 (NOT 47.5) ppm in both rats and mice AND the systemic toxicity NOAEL was at least 5 (NOT 4.75) ppm in both rats and mice.
- In the draft report, PPS in male rat and mice offspring was incorrectly reported as having a NOAEL of 4.75 ppm. According to a covariate analysis (adjusted for body weight at acquisition or for body weight on PND 14, since body weight and age at PPS are clearly related), PPS was delayed only at 7,500 ppm (500 mg/kg/day) in rats and at 3,500 ppm (500 mg/kg/day) in mice. Therefore, the NOAEL is 750 ppm (50 mg/kg/day) in rats and 300 ppm (50 mg/kg/day) in mice. The exact same effect levels and NOAELs were present for acquisition of vaginal patency (VP) in offspring females when covaried by body weight in both rats and mice.

Response: DfE agrees that the target doses should be used rather than the recalculated doses when determining the reproductive toxicity hazard of BPA. As a result, the NOAELs used to designate hazard level (e.g., the Tyl studies) have been revised. DfE determined that there are multiple, distinct endpoints with NOAELs in the Moderate hazard range (50-250 mg/kg bw-day) and LOAELs in the Low hazard range (>250 mg/kg bw). Although the 50 mg/kg bw-day NOAELs are on the border between High and Moderate hazard, the inclusion of the results from BMD modeling, as described in the NTP Expert Panel review, also support the Moderate hazard

designation. The benchmark dose lower confidence limits (BMDLs) were added to the study summary and the hazard summary statement was edited to reflect these changes.

Comment: The summary paragraph for the reproductive effects section of the BPA hazard profile refers to “considerable uncertainty” regarding effects reported in recent studies at oral doses <5 mg/kg bw-day. As for carcinogenicity, uncertainty is not the same as hazard and provides no basis for any reproductive toxicity hazard designation.

Response: This statement was removed from the hazard summary statement. It should be noted that the summary paragraphs are designed for a wide-ranging audience. While the phrase “considerable uncertainty” was deemed to be useful for non-technical stakeholders, the comment correctly identifies that the phrase may be interpreted differently by other readers.

Developmental Toxicity of BPA

Comment: Developmental toxicity has a High hazard designation in the BPA hazard profile based on “suggestive evidence” for neural and behavioral alterations, as reported in the NTP-CERHR (2008) and FAO/WHO (2011) reports. The specific comments from these reports indicate effects reported at low doses in certain studies that are associated with a high level of uncertainty. The hazard designation is then characterized as “High concern, with a lower confidence.” However, the meaning of “High concern, with a lower confidence” is not clear. The EPA hazard evaluation criteria document does not have such a designation. The criteria document sets general requirements for use of the GHS criteria and data evaluation approach, EPA risk assessment guidance, EPA High Production Volume (HPV) Challenge Program, and the Organisation for Economic Co-operation and Development (OECD) HPV Programme data adequacy guidelines. With application of these requirements, it is not clear how “suggestive evidence” with high uncertainty can support any hazard designation.

Response: The NTP-CERHR (2008) and FAO/WHO (2011) expert panel review reports were used as the basis for this hazard evaluation. Both documents highlight uncertainty regarding developmental effects associated with low dose (<50 mg/kg-day) exposure. The NTP-CERHR and FAO/WHO reports comment on the strength of the evidence and not the potential potency of the chemical. DfE Alternatives Assessment Criteria for this endpoint are threshold-based, thus incorporating the potency of a chemical. Based on the expert panel review reports, DfE continues to believe that High concern is the appropriate hazard designation for this endpoint, since there are studies documenting effects at doses below 50 mg/kg bw-day that cannot be discounted. The qualifying statement “with lower confidence” has been removed. There will be no changes to the hazard profile based on this comment.

Comment: The draft hazard profile for BPA is outdated and fails to incorporate recent and highly relevant studies. Significant studies have been conducted subsequent to the completion of the NTP-CERHR (2008) report, including data from EPA. For neural and neurobehavioral effects, which appears to be the basis for a High developmental toxicity hazard designation, the new data would support a Low hazard designation.

Response: The BPA literature on developmental toxicity is extensive and continues to evolve. The NOAELs and LOAELs contributing to the hazard designation have been published in independent expert panel review reports including NTP-CERHR (2008) and FAO/WHO (2011). Using a hazard-based approach, DfE methodology is consistent with the use of these high-quality values. In the absence of definitive evidence to the contrary, more recent studies are not anticipated to alter the assigned hazard designation. If an authoritative body revises the assessment of high value studies that results in changes to threshold values and/or weight of evidence, then DfE may consider revising hazard designation accordingly.

Comment: FDA human health judgments on BPA should also be applied to the developmental hazard designation. From FDA's extensive documentation, a NOAEL of 50 mg/kg bw-day would result in a Moderate developmental hazard designation. This value is also consistent with the many regulatory agencies worldwide that have reviewed BPA in detail (e.g., European Food Safety Authority, European Union risk assessment, Japanese risk assessment).

Response: FDA has clearly stated that it supports the conclusions of the NTP-CERHR (2008) evaluation, which is the basis for DfE's hazard evaluation. Specifically, FDA states "Studies employing standardized toxicity tests have thus far supported the safety of current low levels of human exposure to BPA. However, on the basis of results from recent studies using novel approaches to test for subtle effects, both NTP and FDA have some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children."

Comment: If the NTP-CERHR (2008) BMD approach is used, the BPA concentrations at which there are no reproductive or developmental effects are greater than 50 mg/kg/day (perhaps as high as 100 or 150 mg/kg/day). Defining lower NOAELs (and LOAELs) on the basis of "suggestive evidence" and "uncertainties" violates the scientific basis for calculating these levels, and results in much lower and inaccurate NOAELs and LOAELs, and an inappropriate classification of BPA as a High hazard. The scientific reality is that the reproductive/postnatal NOAELs in our studies are at or greater than 50 mg/kg-day for both rats and mice based on our multi-generational dietary studies, which result in the classification of BPA as a Medium or Low hazard.

Response: Where the intent is to communicate potential hazard concerns, EPA believes that the use of suggestive evidence is appropriate. DfE has stated in partnership documents that the developmental toxicity as well as the reproductive toxicity hazard designations for BPA will be based on the NTP-CERHR (2008) and FAO/WHO (2011) expert panel review reports. Using a hazard-based approach, the inclusion of BMDs and BMDLs in the developmental endpoint section do not change the hazard designation for the developmental endpoint because concern remains for effects occurring at doses <50 mg/kg-day.

The NOAEL for reproductive effects was changed based on the results of BMD modeling.

Comment: BPA's High designation for reproductive and developmental human health effects in Table 4-4 is concerning. Studies have found that BPA is not a primary or selective reproductive or developmental toxicant in the two most commonly used animal models (rats and mice). It only causes adverse reproductive and/or developmental effects at the most toxic BPA dose to the

parental animals, with no reproductive or developmental effects at any of the lower doses including the next lowest dose which was also systemically toxic to the parents. Effects on reproduction and/or offspring development are observed ONLY in the presence of profound adult systemic toxicity at very high BPA dietary doses.

Response: The NTP-CERHR (2008) expert panel review report concludes that there is suggestive evidence of neural and behavioral alterations in rats and mice with NOAELs ranging from 0.01-0.2 mg/kg-bw/day, which was used to assign a High concern for developmental toxicity. These studies fall below the threshold value of 50 mg/kg bw/day, which defines chemicals of High hazard designation. All referenced studies are academic investigations published in peer-reviewed literature and address alterations in the development of neurons in the brain and behavior in offspring. The FAO/WHO (2011) report generally emphasizes that there remains uncertainty regarding the interpretation of these data but does not refute the NTP-CERHR (2008) conclusions.

DfE has stated in partnership documents that the developmental toxicity as well as the reproductive toxicity hazard designations will be based on the NTP-CERHR (2008) and FAO/WHO (2011) expert panel review reports. Please note that the BPA literature on developmental toxicity is extensive and continues to evolve. NOAELs and LOAELs have been assigned by independent expert panels (e.g., NTP-CERHR (2008) and FAO/WHO (2011)) and authoritative changes to these values should come from such a venue. The NTP-CERHR (2008) expert panel review report conclusions are a strong basis for the developmental endpoint. A new bisphenol A exposure study currently in progress by the FDA is designed to address past criticisms of previous study limitations. Preliminary results support a High hazard concern for developmental effects.

Neurotoxicity of BPA

Comment: Commenter stated concern about using the structural alert for phenols (BPA) to assign Moderate concern for neurotoxicity (U.S. Environmental Protection Agency 2010) even with a recent negative guideline-compliant published neurotoxicity study (Stump, Beck et al. 2010).

Response: In DfE Alternatives Assessments, the endpoint neurotoxicity, defined as “an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biological agent” excludes consideration of developmental neurotoxicity, which is grouped with the endpoint developmental toxicity. The Stump et al. (2010) study is described in the hazard assessment in the FAO/WHO (2011) study summary for the *developmental toxicity* endpoint. In the absence of experimental data for *non-developmental* neurotoxicity, a structural alert, along with professional judgment, can be used to make an estimated hazard designation.

Ecotoxicity of BPA

Comment: In both the acute and chronic toxicity sections of the ecotoxicity hazard profile for BPA, Wright-Walters et al. (2011) is frequently cited as the source of data presented in these

sections. As described in a recent letter to the editor, this paper has numerous flaws and mistakes and should not be cited at all in the BPA hazard profile. It should be removed.

Response: The majority of studies cited to Wright-Walters et al. (2011) are also cited in Joint Research Centre-Institute for Health and Consumer Protection (JRC-IHCP) (2010). It should be noted that the letter to the editor mentioned by the commenter points out flaws in the calculation of a predicted no effect concentration (PNEC) – a value that is not used in a DfE Alternative Assessment. Given that other reporting inconsistencies would have been identified through evaluation of and comparison to the JRC-IHCP (2010) review, no change to the hazard designation is required.

BPS

Comment: Mistake in the units regarding water solubility of BPS. EPA needs to check to make sure that this does not impact any estimation.

Response: The water solubility units for BPS (CASRN 80-09-1) have been corrected. The correct water solubility value of 1,100 mg/L was used with the Estimation Programs Interface (EPI) estimation program during the assessment process; therefore, no subsequent estimations were impacted.

Water Solubility (mg/L)	1.1x10 ³ (Measured) Reported as 1.1 g/L at 20°C	ECHA, 2011	Adequate, nonguideline study reported in secondary source; value is consistent with other reported properties.
	<2x10 ³ (Measured)	HSNO, 2010	Inadequate; sufficient details were not provided to assess the quality of this study.

TGSA

Comment: Two comments were submitted regarding the skin sensitization hazard designation assigned to TGSA in relation to the July 2012 Chemicals Evaluation and Research Institute (CERI) report. Specific points include:

- Skin sensitization for TGSA should be changed from High to Low based on findings from a guinea pig maximization test (GMPT) test showing TGSA is a “weak” sensitizer and not as a “strong sensitizer” in the July 2012 CERI report.
- The draft report gives a High hazard designation for skin sensitization for TGSA. Actual test data from the report CERI Evaluation for Outcomes from Different Skin Sensitization Test (TGSH) supports the position that the GPMT results were “Positive”. A “Positive” response however requires an interpretation using Table 1-1 (Page 6 of the report) based on the response of 70% using an intradermal dose of 50% (also interpreted in Table 2 Page 7 as “1B”); the correct interpretation is that TGSA is in fact a “weak” skin sensitizer. This is further supported by the negative responses with the Buehler test (BT) and local lymph node assay (LLNA) tests. Based on the correct interpretation of the skin sensitization data, the skin sensitization rating should be Low, or at worst case, Moderate.

Response: The hazard designation for skin sensitization for TGSA was changed from High to Moderate based on a weight-of-evidence approach for skin sensitization. The hazard summary

statement was revised to reflect that TGSA was categorized as a weak skin sensitizer based on test concentrations and positive incidence rates in the guinea pig maximization test. These results, along with negative responses for the BT and LLNA tests, warrant a Moderate hazard designation.

Comment: Two comments were submitted regarding the respiratory sensitization hazard designation assigned to TGSA. Specific points include:

- Respiratory sensitization for TGSA should be left out of the report and revisited when more data is available since it states that “there are no standard test methods for respiratory sensitization; as a result there was often no designation for this endpoint.”
- Commenter maintains that TGSA will oxidize easily so it is unlikely to be respiratory sensitizer. It was also claimed that metabolism would be required, and that in 25 years of production there has been no indication of sensitization in workers.

Response: DfE does not agree with these comments. As stated in Chapter 4, DfE may rely on the presence or absence of structural alerts to characterize concern for chemicals that lack test data. TGSA contains a structural alert associated with respiratory sensitization (terminal double bond).

Comment: Two comments were submitted regarding the aquatic toxicity hazard designation assigned to TGSA. Specific points include:

- Chronic aquatic toxicity for TGSA should be changed from High to Moderate. A study titled “A study of TGSA in Medaka” published by CERI found a lowest observed effect level (LOEC) and no observed effect level (NOEC) of >8.0mg/L and >= 8.0mg/L, respectively. A rating >1.0mg/L would be considered Moderate based on the DfE’s rating guidelines.
- The draft report gives a High hazard designation for chronic aquatic toxicity for TGSA. Actual test data from the report Class 9 Chronic test Medaka 2011 09 conducted and prepared by CERI in accordance with “OECD Good Principles of Laboratory Practice”, Test Method OECD 215 using Guidance Document 23 supports a chronic aquatic toxicity rating of Moderate. The results of the report provide a LOEC >8.0 mg/L and a NOEC >8.0 mg/L.

Response: The study in *Oryzias latipes* (Medaka) was added to the hazard assessment. The hazard designation for chronic aquatic toxicity has been changed from High to Moderate based on experimental NOEC/LOEC and chronic half maximal effective concentration (EC₅₀) values for fish and daphnia that fall within the 1.0-10 mg/L range.

Comment: Repeated dose effects for TGSA should be changed from High to Moderate. DfE extrapolated a 28-day study to 90-days to meet its standard criteria. A commenter extrapolated the thresholds and found it to fall into the Moderate category. The commenter also recommends that additional studies be conducted at the 90-day guideline to eliminate the need for extrapolation.

Response: The repeated dose effects hazard designation for TGSA will remain High. The DfE Alternatives Assessment Criteria thresholds are for 90-day duration studies. The NOAEL for this 28-day study is 15 mg/kg-day and the LOAEL is reported as 150 mg/kg-day. To extrapolate

from a 28-day to a 90-day study, threshold values must be tripled. Hence the threshold values for hazard designation are High: < 30 mg/kg-day, Moderate: 30-300 mg/kg-day, and Low: > 300 mg/kg-day. Based on the NOAEL, the hazard designation is High. There is also a structural alert for liver and kidney toxicity based on the potential for the formation of epoxide oxidation products. The extrapolation of the 28-day study was clarified in the data quality section for this study.

D-8

Comment: Genotoxicity potential for D-8 should be changed from Moderate to Low for D-8. Based on an *in vitro* study Nippon submitted in its 1987 Premanufacture Notice (PMN), authors concluded that "...no evidence of mutagenic potential of D-8 was obtained in this bacterial test system at the dose levels used."

Response: Additional genotoxicity data were added to the hazard assessment. The hazard designation for genotoxicity was changed from Moderate to Low.

Comment: Repeat dose effects for D-8 should be changed from High to Moderate. The current hazard designation is based on BPS as an analog. A commenter has provided empirical repeat dose effect data for D-8.

Response: After receipt and review of the 90-day study, the data were added to the hazard assessment in the repeated dose effects section. The hazard designation for the repeated dose effects endpoint was changed from an estimated High (based on analogy to BPS) to an experimental Moderate (based on a NOAEL of 50 mg/kg-day).

A review of summary data submitted to ECHA and posted on the ECHA website (<http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>) resulted in an update of the hazard designations of three endpoints. Acute aquatic toxicity was changed from estimated High to measured High; persistence was changed from estimated Moderate to measured Moderate; and bioaccumulation was changed from estimated Low to measured Moderate.

D-90

Comment: Bioaccumulation for D-90 should be changed from High to Low. It is currently based on estimated data but Nippon has provided a bioaccumulation study from its 1998 PMN (Study # 7B284G). It is based on a carp bioconcentration factor (BCF) <2 for the high exposure and <19 for the low exposure.

Response: D-90 is a polymeric mixture of two components (where n=1 and n=2). The component with the highest hazard potential is used to assign the hazard designation for each endpoint of the alternative assessment. The estimated bioaccumulation factor (BAF) for D-90 from EPI for the n=2 component is >1,000, resulting in a High bioaccumulation hazard designation.

The bioaccumulation study data referred to in this comment were reviewed and evaluated. It should be noted that the reported values are not experimental measurements for D-90 and are based on data for a supporting substance (structural analog or surrogate). According to the DfE Alternatives Assessment Criteria, in the absence of experimental data for an alternative, the quantitative structure–activity relationship (QSAR)-based estimations from the EPA New Chemicals Program’s predictive methods will be used preferentially to analog data for performing evaluations. Estimated values derived from other sources are generally not included in the report. The bioaccumulation hazard designation for D-90 will remain High based on these estimates.

Pergafast 201

Comment: The wording for the NOAEL for reproductive toxicity of Pergafast 201 as stated on the Table on page 4-387 should be changed. Currently, the NOAEL is identified as “NOAEL (F1 pups): ≥ 200 mg/kg bw-day”. This can be misread to relate to developmental effects, which are described on the following page and indicate a NOAEL of 100 mg/kg based on F1 pups. The two statements appear to conflict. Clarity can be achieved by changing to NOAEL for reproductive toxicity to “NOAEL: >200 mg/kg bw-day based on fertility”.

Response: In response to the comment, OPPT toxicologists reviewed and revised the study summary to clarify the designation of Moderate concern for reproductive toxicity. The summary now states that there was a decrease in implantation sites at the highest dose, which the decrease was not statistically significant, but toxicity cannot be ruled out at doses between 200 and 250 mg/kg.

This review also led to an update of the developmental toxicity data and a revision to that hazard designation, as well. The hazard designation for developmental effects is now High, based on decreased pup viability at 50 and 100 mg/kg.

Comment: Algal toxicity for Pergafast 201 should be changed from Very High to Moderate based on two studies previously provided to EPA: one in which algae were exposed to Pergafast 201 under static conditions according to the OECD 201 Testing Guideline, and a second in which algae were exposed to Pergafast 201 in the presence of sediment to mimic realistic conditions (described as second study listed for Green Algae – confidential submission).

Response: In response to the comment, OPPT toxicologists changed the acute aquatic toxicity hazard designation for Pergafast 201 to High based on consideration of the toxicity values reported in these studies for algae. The chronic aquatic toxicity hazard designation for Pergafast 201 will remain High also based on the chronic toxicity values calculated for algae.

Comment: Data on toxicity to terrestrial plants for Pergafast 201 is available. The commenter understands that DfE does not include this in the assessment but feels that the results illustrate Pergafast 201’s lack of impact on the environment.

Response: A row presenting information on terrestrial ecotoxicity was added to the Pergafast 201 hazard profile with Earthworm Subchronic Toxicity and Toxicity to Terrestrial Plants as

endpoints. The study summary for the terrestrial plants toxicity was also added to the assessment profile.

II. Comments on Other Report Content

Comment: Lack of overall rating of alternatives needs to be more transparent. Some readers are confused into thinking that there is a list of recommended substances where one is not apparent. This should be emphasized in the preface of the document.

Response: DfE revised Section 1.2 to emphasize that the report does not provide a ranking of alternatives by preferability or provide guidance on the appropriate use of BPA or other alternatives; rather the information provided in this alternatives assessment is meant to assist decision makers in better understanding the BPA and its potential chemical alternatives in thermal paper.

Comment: There is a section of the analysis where EPA mentions that Japan banned BPA, but the report also includes discussion of “design challenges for companies” and “substitution issues.” One question that came up to many readers was, “if Japan could do it, why is it such a problem for EPA to deal with it?” Another comment frequently mentioned was “we didn't need BPA in containers and papers at various other points in society, so why is it needed now?” The report could address these issues in a direct way.

Response: DfE added a discussion of the regulation of existing chemicals under the TSCA, which puts the burden of proof on EPA to demonstrate that a chemical poses an unreasonable risk.

Comment: Four comments were submitted regarding the proprietary chemical included in Table 3-3 on page 3-8 of the report. Specific points include:

- There are other chemicals with “unknowns” next to them. What do those mean?
- There is a “proprietary” chemical whose presence is stated as “unknown.” First, what does that mean in practice for industry, and how is EPA to communicate that? Second, if a chemical is so important as to not be released in structure or even family name, how is it not important enough to know whether it has been in thermal paper or not? The response/information submission seems questionable, at best.
- The proprietary chemical in Table 3-3 has “proprietary” under its status of use in thermal paper. This may lead the reader to assume the chemical is used.
- The report includes data on two proprietary mixtures and EPA should better explain the limitations.

Response: For many alternatives, EPA simply does not know if the chemical is currently in use. The chemicals in this report have been included because stakeholders have indicated that the chemicals may be used in thermal paper based on their structures and properties. In Table 3-3, DfE changed “proprietary” to “unknown” for consistency and to better reflect the chemical’s actual status, which is that EPA does not know if it is in use or if is included for research and development purposes.

Under TSCA, companies may claim confidentiality for proprietary information and DfE must protect these confidentiality claims in its alternatives assessments. As part of its commitment to increase transparency and public access to chemical information, EPA encourages the release of confidential information once the chemical's intellectual property protections are in place. An explanation of the relationship between DfE and TSCA has been added to the report.

Comment: In Chapters 5 and 6, there are allusions to the issues surrounding BPA releases more generally, and also in particular streams, but it would be helpful if there was more explicit mention as to the fact that BPA sources are numerous and that thermal paper is not necessarily always the specific source to be considered in each waste management/end-of-life stage. Is BPA the major contributor to these sources? Do we know? How does one connect the releases to the source?

Response: DfE reviewed Chapters 5 and 6 and clarified, as necessary, that the sources of BPA are numerous and it is not known to what degree thermal paper is contributing to releases.

Comment: On page 6-3, EPA states that "Several chemicals included in this analysis appear to have more preferable profiles, with low human health and ecotoxicity endpoints" but it does not name these chemicals. The report clarifies that these determinations were not based on empirical data, rather modeling and expert judgment.

Response: DfE acknowledges the comment and no change to the report is required.

Comment: Chapter 6 discussion of deforestation due to sales receipts leads public to believe that the production of point of sale (POS) contributes to deforestation and that 9.6 million trees are cut down every year to satisfy the POS market need. A review of literature indicates that the pulp and paper and allied industries are not a major contributor to defores

Response: DfE edited the text to clarify that studies show the paper industry is not believed to be a significant cause of deforestation.

Comment: Chapter 6 discussion of deforestation due to sales receipts and the use of e-receipts lead the public to believe that e-receipts offer a greener/healthier alternative than paper receipts because of less paper waste (and less cutting down of trees) and less of exposure to BPA/other chemicals. The use of electronics may use more chemicals, fossil fuels, and energy than paper production. Remove the closing paragraph of Section 6.7 on page 6-11 and an invitation to industry, governmental agencies and academia to collaborate, innovate and promote "greener" developer technologies than BPA and its analogs.

Response: DfE has revised the language regarding electronic receipts and states that a full life-cycle analysis (LCA), which is outside the scope of this assessment, would be needed to compare e-receipts to thermal printing.

Comment: The report provides little information about the magnitude of chemical use for the thermal paper market in the U.S., but states that 9.6 million trees are cut in the U.S. alone to supply receipt paper. BPA or replacement color developers are coated on the exterior of thermal

paper in relatively large amounts but are not bound tightly to the paper surface. The largest U.S. maker of thermal paper, Appleton Paper, announced that it had switched from BPA to BPS in 2006.

Response: DfE acknowledges the comment and agrees that information on the magnitude of chemical use for the thermal paper market in the U.S. would be useful to the report. Unfortunately, information on the amount of BPA and its alternatives used in thermal paper is not publically available.

Comment: The report appears to promote the use of alternative printing technologies as an intrinsically safer method for sales records, labels, and images. DfE's draft alternatives assessment rates each of the 19 alternatives as High or Very High concern for at least one human health or ecological endpoint, raising the question of whether there is any suitable way to make thermal paper. DfE assessments should clearly identify chemicals that achieve a higher level of safety, as was recently done in the review of alternatives for NPEs.

Response: DfE does not typically judge which chemicals evaluated in an alternatives assessment are safer alternatives. DfE did so for NPEs based on experience and criteria developed under the Safer Product Labeling Program, an advantage not available for thermal paper. DfE Alternatives Assessments are intended to provide the best information from testing and modeling to support decision making by the stakeholder community. In addition, a full LCA, which is outside the scope of this assessment, would be needed to compare e-receipts to thermal printing.

Editorial Comments

Comment: A number of commenters suggested edits to specific text in the report to improve clarity.

Response: DfE reviewed suggested edits and incorporated the suggestions into the revised draft report as appropriate.

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