NTP Research Concept: Bisphenol S

Project Leader

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Background and Rationale

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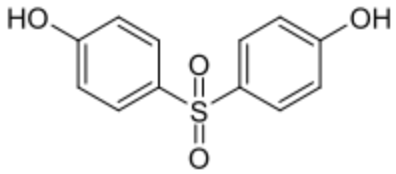


Bisphenol S (BPS) was nominated by the National Institutes of Environmental Health Sciences (NIEHS) and the Environmental Protection Agency (EPA) to the National Toxicology Program (NTP) for toxicological evaluation based on its extensive use, high potential for human exposure, possible endocrine activity, and limited toxicity data. BPS, and BPS derivatives (chemicals with the same core sulfone structure as BPS, such as TGSA and BPS-MAE, see table), are increasingly used as replacements for Bisphenol A (BPA) in the production of polymers (e.g. microwave dishes, baby bottles, artificial organs, dialyzers, coatings, etc.) as well as a raw material in the preparation of a number of products (e.g., developers for heat sensitive paper, fire retardants, intermediates for colorants, pharmaceuticals, pesticides, etc.). It is a high production volume chemical with an aggregate production of 1 to 10 million pounds (2012).[1]

BPS is structurally similar to BPA and exposures can occur through multiple routes: oral, dermal, inhalation, blood and/or tissues (with use of dialyzers or artificial implants); however, primary exposure likely occurs through the oral route. BPS has been recorded in food (e.g. cereals, seafood, dairy, vegetables, canned products, meats), indoor dust, sediment and paper products (e.g., toilet paper, cashier's receipts, currency).[2,3,4,5,6] It is moderately persistent in sediment and has the potential for accumulation in aquatic environments. Additionally, BPS has been found in 81% of the human urine samples analyzed, from general populations in the United States and several Asian countries, at concentrations ranging from below the limit of quantitation to 21 ng/mL (mean concentration of 0.654 ng/mL).[7]

BPS has been assessed in a number of *in vitro* assays as part of the NTP's Tox21 High Throughput Screening Program (HTS), where it was classified as an estrogen agonist with some affinity for the estrogen receptor based on activity in two estrogen receptor binding assays and one receptor activation study (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6626). Quantitative

structure-activity relationship (QSAR) analyses performed using GeneGo models predicted carcinogenic, hepatotoxic, nephrotoxic, and neurotoxic effects of BPS, as well as anemia. The QSAR-predicted molecular targets that were identified by GeneGo including inhibition of MMP-13, stromelysin 1, transthyretin, and estrogen receptors; these targets indicate that BPS could affect embryonic development, reproduction, tissue remodeling, thyroid hormone (T_4) and retinol transport, and normal estrogen function. Although the QSAR-predicted targets and effects of BPS require confirmation, they appear to be compatible with the available toxicity data.

Currently, there is insufficient *in vivo* toxicological data to adequately characterize the possible human health effects of BPS (data are limited in scope and power and has not been peer reviewed); however, of the limited toxicological data (primarily available form industry), there is evidence that BPS has effects on select organs and hematological factors. Rats administered BPS via oral gavage for 28 days displayed a decrease in body weight gain and food consumption, gastrointestinal findings (hemorrhage and abdominal distension), changes in organ weights (liver, thymus, and adrenal gland weights) as well as effects on hematological parameters (i.e., changes in red blood cell count, hemoglobin, hematocrit). Similar findings were observed in a 13-day dietary administration study where adverse changes in liver, kidney, and body weights as well as hematological parameters were observed. Adverse reproductive and developmental effects were noted in a short-term oral administration study in male and female rats where body weight gain was suppressed, liver weights were increased, fertility was impacted, and a decrease in the numbers of live births and offspring were observed.

Metabolism, disposition, and toxicokinetics data for BPS are not available for rodents or humans. Additionally, assessments of chronic toxicity, immunotoxicity, carcinogenicity, developmental, and reproductive studies have not been performed or are very limited in nature.

Key Issues

Short-term exposure information and QSAR analyses suggest that BPS may have endocrine activity, organ toxicity, and effects on hematological factors. QSAR evaluation predicts both carcinogenic and neurotoxic effects; however, studies addressing these concerns have not been conducted. Recent increases in human exposure to BPS suggests that an evaluation of BPS, following oral exposure, to characterize potential toxicities is warranted and should include a determination of the kinetics, absorption, distribution, metabolism, and excretion profiles of BPS; appropriate caging materials (BPS is used as a replacement for BPA in plastics); route of exposure (dietary or gavage); and understanding the critical window of exposure for reproductive and developmental concerns in the young animal would provide essential data for evaluation of BPS.

Additionally, BPS derivatives (e.g. TGSA, BPS-MAE, BPS-MPE, D-8, and D-90) and analogues (e.g. BPA, Bisphenol AF) share a high degree of structural similarity (see table below) and exhibit estrogenic activity in HTS. However, it is not feasible to comprehensively assess the toxicological profile of each derivative and analogue;

therefore, surveying the current HTS data to evaluate structural and biological similarities, utilizing additional endocrine *in vitro* assays (including non-mammalian) and evaluating *in vivo* data from current programs (BPAF, BPA CLARITY project[8]) will allow identification of specific endpoints that may be useful for an assessment of the bisphenol family and provide a better understanding of this class of chemicals.

Specific Aims

- Characterize the dose-response effects of oral exposure to BPS on target organ systems with a focus on reproductive, developmental, neurological, and hematological endpoints.
- Assess *in vivo* absorption, distribution, metabolism, excretion, and toxicokinetic (ADME/TK) profiles for BPS and *in vitro* clearance and metabolism information for BPS and each of the BPS derivatives (with a focus on understanding the core BPS structure).
- Determine the need for chronic toxicology studies based on target organ toxicity (e.g., carcinogenic evaluation of BPS).
- Compare and contrast BPS *in vivo* and *in vitro* data with other analogues and derivatives to build a knowledge base of bisphenol chemicals.

Proposed Approach

Phase 1

1) Leverage initial NTP efforts (evaluation of *in vitro* and HTS data on multiple bisphenol analogues for similarity profiling and endocrine activity) for preliminary toxicological profiling.
2) ADME/TK characterization in rodents: oral and intravenous exposure of BPS and metabolism characterization of BPS derivatives.
3) *In vivo* toxicity evaluation of BPS in rodents:
   Perinatal oral exposure dose range finding study
   Short-term adult oral exposure toxicity study

Phase 2

1) *In vivo* toxicity evaluation of BPS in rodents:
   Subchronic oral including perinatal exposure window to assess potential for reproductive toxicity, teratogenicity, and neurotoxicity.
   Adult oral exposure 90-day toxicity study.

Phase 3

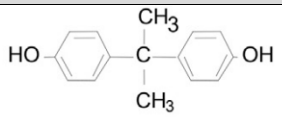
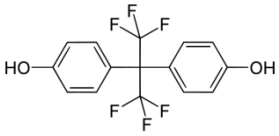
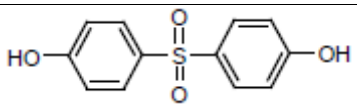
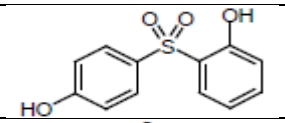
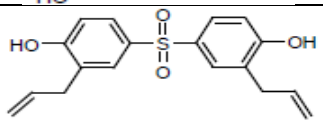
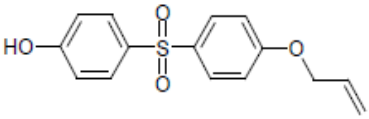
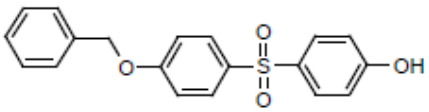
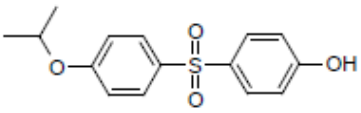
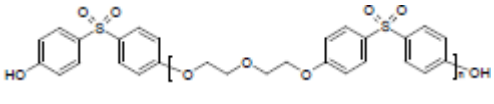
1) Additional studies, as needed (e.g., carcinogenicity, immunotoxicity).
2) Utilizing *in vitro* and *in vivo* data to compare and contrast select analogues.

Significance and Expected Outcome

There is a considerable amount of data available on BPA toxicities; however, very little is known about the potential replacement chemicals. Therefore, the proposed studies for BPS (a known replacement for BPA) will address considerable data gaps for a high production volume chemical that has been measured in human urine, found in environmental samples, and appears to target hepatic, renal, hematological, reproductive, and developmental endpoints. *In vitro* and ADME/TK information will produce data for a comparison between BPS and derivatives (and possibly about the core sulfone structure) and *in vivo* dose-response data on BPS will provide information for a risk assessment of BPS and evaluation of human exposure and observed toxicities in a rodent model.

As previously mentioned, BPS, and other BPA analogues, have been recorded in food, dust, sediment, and paper products suggesting that the public is routinely exposed to a variety of bisphenols. The prevalent nature and high exposure potential of these chemicals suggest that a more global understanding of the effects of bisphenol chemicals would be beneficial, especially in a developing child. The NTP has spent considerable efforts characterizing the effects of other analogues (BPA, BPAF) and inclusion of the BPS studies will allow for a comprehensive comparison of *in vitro*, including HTS information, and *in vivo* data for an evaluation of class effects. Assessments would include comparing and contrasting analogue structural and biological similarities, endocrine activity, toxicities, mechanisms of action, and *in vitro* versus *in vivo* effects, as well as human exposure data from the National Institute for Occupational Safety and Health (NIOSH) and/or National Health and Nutrition Examination Survey (NHANES). This multifaceted approach will potentially allow for a bridging of information across BPA analogues and possibly allow for a better risk assessment of bisphenols in general.

Table: Names and structures of select BPA analogues and derivatives of BPS are listed below. Hazard characterization for BPA and BPAF is currently ongoing. BPS (and derivatives) is under consideration for evaluation due to its extensive use, high potential for human exposure, possible endocrine activity, and limited toxicity data.

BPA and BPA Analogues: Chemicals with similar properties and/or altered chemical structure that are structurally similar to BPA	**Structure**
BPA Bisphenol A CASRN: 80-05-7	
BPAF Bisphenol AF CASRN: 1478-61-1	
BPS Bisphenol S CASRN: 80-09-1	
BPS Derivatives: Chemicals derived from BPS, with the same core sulfone structure (O=S=O) as BPS.	
2,4-BPS (2,4'-Bis(hydroxyphenyl)sulfone) CASRN: 5397-34-2	
TGSA (Bis-(3-allyl-4-hydroxyphenyl) sulfone) CASRN: 41481-66-7	
BPS-MAE (Phenol,4-[[4-(2-propen-1-yloxy)phenyl]sulfonyl]) CASRN: 97042-18-7	
BPS-MPE (4-Hydroxy-4'-benzyloxydiphenylsulfone) CASRN: 63134-33-8	
D-8 (4-Hydroxyphenyl 4-isoprooxyphenylsulfone) CASRN: 95235-30-6	
D-90 (4-[4'-[(1'-methylethyloxy) phenyl]sulfonyl]phenol) CASRN: 191680-83-8	

References

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Analogues in Foodstuffs from the United States and Their Implications for Human Exposure. J. Agricultural and Food Chemistry, 2013. 61, 4655−4662.

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