

**AUDIT OF LITERATURE CITED AND FIDELITY OF
REQUESTED CHANGES TO DRAFT BISPHENOL A
EXPERT PANEL REPORTS**



National Toxicology Program



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BACKGROUND

In a letter dated March 26, 2007 from Dr. David Schwartz, Director of the National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP), to Representative Henry Waxman and Senator Barbara Boxer, Dr. Schwartz pledged to carry out a review of the Sciences International, Inc. (SI) contract and the nature of the services provided by SI to the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR). As part of this review, there was an audit of two key activities carried out by SI: (1) selection of literature relevant for review by the expert panel on bisphenol A (BPA) and (2) incorporation of input from expert panel members into draft reports. The first task of the audit was to conduct an independent survey of the literature on BPA to identify references and compare them with the list selected by SI to summarize in the initial August 2006 draft expert panel report and with the total bibliography considered by SI and the expert panel during development of the first three drafts (August 2006, December 2006, March 2007) of the expert panel report. The second task was to audit the fidelity with which changes requested by expert panel members were incorporated into the December 2006 and March 2007 draft expert panel reports by SI staff.

PART 1. LITERATURE REVIEW

Strategy

The literature review was designed to identify references that were not included in the draft reports, but might have been considered important for the BPA evaluation. Two sets of references were screened for this purpose.

First, staff from the NIEHS library carried out a search of PubMed using the search terms bisphenol and the Chemical Abstract Service number for BPA (80-05-7). This all-inclusive search identified 4900 references. NTP staff screened the titles of all 4900 citations to identify ones seemingly relevant to the deliberations of the expert panel for carrying out its specific charge of determining whether BPA is a hazard to human reproduction and/or development. References (set 1) related to the following topics were selected:

- Reproduction and development (*in vivo* and *in vitro*), animal and human studies
- *In vivo* measures of estrogenicity in relevant species
- Absorption, disposition in the body, and metabolism during pregnancy
- Body burden when related to pregnancy/children
- General toxicity
- Studies of BADGE, BISGMA, BIS-DMA (chemicals with a BPA core structure) included if related to reproduction/developmental toxicity
- Immunological or neurological measures not resulting from exposure during development
- Studies in non-traditional species that included (1) developmental exposure and/or (2) endpoint(s) related to reproductive organs or function

- *In vitro* assays of estrogenicity (excluding estrogen receptor binding/transcriptional activation/cell proliferation/yeast variants)
- *In vitro* estrogen response genes in cells from reproductive organs
- Comparisons of batteries of *in vitro* screens for estrogenicity
- Vitellogenin (protein produced in oviparous vertebrates in response to estrogens)

NTP staff identified a second set of references from a web site that lists literature citations pertaining to BPA with specific emphasis on studies that demonstrate biological activity at doses lower than those used in traditional toxicology studies. This web site (<http://endocrinedisruptors.missouri.edu/vomsaal/vomsaal.html>) is maintained by Dr. Fred vom Saal, a researcher active in the field at the University of Missouri. NTP staff reviewed the titles and abstracts of these references and identified ones of potential relevance to the BPA evaluation.

NTP staff compared the collective, unique citations from these two sets against the bibliography of 447 references in the August 2006 draft of the expert panel report and against the larger list of 742 references (includes the 447) made available by SI for the panel's consideration at all stages during development of the 3 draft reports (August 2006, December 2006, and March 2007).

Findings

The comparison of citations against the bibliography in the August 2006 draft identified fewer than 100 references considered of potential relevance, but not included in the August 2006 draft report. Approximately 50 citations were for papers published in 2005 or before and the remaining was for papers published in 2006 and 2007 presumably after the initial SI literature search. The expert panel added 9 of these references to subsequent drafts of the report (December 2006 and March 2007).

The second comparison of citations against the list of 742 references identified fewer than 50 papers not cited in the August, December, or March draft reports. NTP staff reviewed these references for their potential relevance to the BPA evaluation. Eliminating abstracts, papers not in English, and papers dated 2007 that may have been published subsequent to the final literature search done for the March 2007 draft, left 5 papers considered of potential relevance.¹ CERHR

¹ Ashby J, Lefevre P (2000) The peripubertal male rat assay as an alternative to the Hershberger castrated male rat assay for the detection of anti-androgens, oestrogens, and metabolic modulators. *Journal of Applied Toxicology* 20:35-47.

Nakamura K, Itoh K, Yaoi T, Fujiwara Y, Sugimoto T, Fushiki S (2006) Murine neocortical histogenesis is perturbed by prenatal exposure to low doses of bisphenol A. *Journal of Neuroscience Research* 84:11197-1205.

Schmidt S, Degen G, Seibel J, Hertrampf T, Vollmer G, Diel P (2006) Hormonal activity of combinations of genistein, bisphenol A and 17beta-estradiol. *Archives of Toxicology* 80:839-845.

Shin B, Kim C, Jun Y, Kim D, Lee B, Yoon C, Park E, Lee K, Han S-Y, Park K, Kim H, Yoo S (2004) Physiologically based pharmacokinetics of bisphenol A. *Journal of Toxicology and Environmental Health, Part A* 67:1971-1985.

has now provided these 5 papers to the expert panel members for their consideration and discussion at the second BPA expert panel meeting on August 6-8, 2007.

PART 2. RECORD OF REQUESTED CHANGES TO THE DRAFT EXPERT PANEL REPORTS DATED DECEMBER 2006 AND MARCH 2007

Strategy

The second part of the audit was carried out by an independent company working under an existing contract to the NIEHS for the purpose of performing data audits. Dynamac Corporation audited e-mail records that pertained to requests from expert panel members for changes to the August 2006 and December 2006 expert panel reports. SI furnished paper copies of the e-mails, separated into received and sent, and in chronological order. Dynamac staff then compared the requests for changes with the changes made. NTP staff then reviewed the Dynamac audit findings.

Findings

This phase of the audit found that all but 6 of the multiple changes requested in over 300 e-mails from the expert panel members were in fact recorded in the draft expert panel reports. These 6 changes have now been made to the expert panel report.

The audit also identified changes in the draft reports that did not appear to track to an e-mail request from an expert panel member. NTP staff reviewed all of the changes. Upon inspection, NTP staff determined that these changes consisted of: (1) formatting errors, (2) addition of literature summaries and tabular entries for new references added to the draft reports as a result of updated literature searches, and (3) corrections to text or tables resulting from the contractor's fact-checking procedures and information received in public comments. These changes were part of the normal editing process for draft reports.

DISCUSSION

Part 1. Literature Review

NTP carried out a review of the literature, independently of SI, to identify references relevant to the expert panel evaluation of BPA. NTP found that SI made available to the expert panel members for their consideration references relevant to the BPA evaluation. NTP identified only 5 additional papers out of the 4900 eligible for consideration that were not included in any of the 3 draft expert panel reports or in the list of 742 references provided by SI to the expert panel for their consideration in development of the December 2006 and March 2007 drafts. These papers have been provided to the panel and will be included in their discussions at the August 6-8 meeting.

NTP also found no evidence for the exclusion of relevant citations by SI in the August 2006 draft expert panel report (the working draft of literature summaries prepared by SI prior to expert panel input). NTP identified nearly 50 papers that were possibly relevant for the deliberations on

Thomas P, Dong J (2006) Binding and activation of the seven-membrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. *Journal of Steroid Biochemistry & Molecular Biology* 102:175-179.

BPA and were published in 2005 or before, but were not represented in the initial August draft report's bibliography. These papers were included in the list of 742 references provided by SI for development of subsequent drafts and the expert panel members chose to add 9 to the December or March drafts.

Part 2. Audit of Expert Panel Changes to Draft Reports

NTP found that SI reliably made changes to the draft reports requested by the expert panel members. The Dynamac audit and response to the audit findings by NTP documented nearly complete fidelity between changes requested by the expert panel and changes appearing in the draft expert panel reports.

CONCLUSION

The audit provides assurance that the draft BPA expert panel reports include consideration of all relevant references and reliably include changes requested by the expert panel members. NTP concludes that the draft expert panel reports are useful for the CERHR evaluation of BPA.