Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis

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\section*{Abstract}

\textbf{Background:} Attention-deficit hyperactivity disorder (ADHD) has increased in prevalence in the past decade. Studies attempting to identify a specific genetic component have not been able to account for much of the heritability of ADHD, indicating there may be gene-environment interactions underlying the disorder, including early exposure to environmental chemicals. Based on several relevant studies, we chose to examine bisphenol A (BPA) as a possible contributor to ADHD in humans. BPA is a widespread environmental chemical that has been shown to disrupt neurodevelopment in rodents and humans.

\textbf{Objectives:} Using the Office of Health Assessment and Translation (OHAT) framework, a systematic review and meta-analysis was designed to determine the relationship between early life exposure to BPA and hyperactivity, a key diagnostic criterion of ADHD.

\textbf{Data sources:} Searches of PubMed, Web of Science, and Toxline were completed for all literature to January 1, 2017.

\textbf{Study eligibility criteria:} For inclusion, the studies had to publish original data, be in the English language, include a measure of BPA exposure, and assess if BPA exposure affected hyperactive behaviors in mice, rats or humans. Exposure to BPA had to occur at $<3$ months of age for humans, up to postnatal day 35 for rats and up to postnatal day 40 for mice. Exposure could occur either gestationally (via maternal exposure) or directly to the offspring.

\textbf{Study appraisal and synthesis methods:} Studies were evaluated using the OHAT risk of bias tool. The effects in humans were assessed qualitatively. For rodents exposed to $20 \mu g/kg$/day BPA, we evaluated the study findings in a random effects meta-analytical model.

\textbf{Results:} A review of the literature identified 29 rodent and 3 human studies. A random effects meta-analysis showed significantly increased hyperactivity in male rodents. In humans, early BPA exposure was associated with hyperactivity in boys and girls.

\textbf{Limitations, conclusions, and implications of key findings:} We concluded that early life BPA exposure is a presumed human hazard for the development of hyperactivity. Possible limitations of this systematic review include deficiencies in author reporting, exclusion of some literature based on language, and insufficient similarity between human studies. SRs that result in hazard-based conclusions are the first step in assessing and mitigating risks. Given the widespread exposure of BPA and increasing diagnoses of ADHD, we recommend immediate actions to complete such risk analyses and take next steps for the protection of human health. In the meantime, precautionary measures should be taken to reduce exposure in pregnant women, infants and children. The present analysis also discusses potential mechanisms by which BPA affects hyperactivity, and the most effective avenues for future research.

\textbf{Systematic review registration number:} Not available.
use (DiFranza et al., 2004), and alcohol consumption (Riley and McGee, 2005) during pregnancy have been associated with the development of ADHD. This is concerning, as rates of ADHD may be increasing in the US (Arnold et al., 2012; Visser et al., 2014; Boyle et al., 2011).

ADHD usually has an onset in early school-aged children and can possibly persist into adulthood (Jain et al., 2017; Kessler et al., 2006), although some evidence suggests that adult ADHD is not associated with diagnosis in childhood (Moffitt et al., 2015). The disorder can affect many behavioral aspects, such as attention (e.g., alertness and vigilance), executive function (e.g., working memory, response inhibition, cognitive flexibility, and planning), and reduced response habituation (Aguiria et al., 2010). ADHD is a heterogeneous disorder, consisting of many symptoms and co-morbidities that are present to varying degrees (Aguiria et al., 2016; Matthews et al., 2014; Baird et al., 2000; Willcutt et al., 2005; Nigg et al., 2005). Individuals with ADHD may also have problematic behaviors/disorders such as aggression, oppositional defiant disorders, conduct disorders, anxiety, depression, substance abuse, sleep disorders, Tourette syndrome, antisocial behaviors, and learning disabilities (Aguiria et al., 2016; Baird et al., 2000; Ramos-Quiroga et al., 2013; American Psychiatric Association, 2013).

Evidence suggests that ADHD is associated with alterations in the prefrontal cortex and dysfunctional monoaminergic signaling in the brain; however, the mechanisms have not been definitively established (Aguiria et al., 2010; Eubig et al., 2010). ADHD is usually treated with a combination of behavioral therapies and stimulant medications that target these signaling pathways, such as methylphenidate and amphetamine (which increase synaptic dopamine release), or norepinephrine reuptake inhibitors, such as atomoxetine (Ramos-Quiroga et al., 2013).

Studies suggest that heritability plays a role in the development of ADHD. Twin studies estimate heritability to be 70–80% (Matthews et al., 2014; Franke et al., 2009; Smith et al., 2009) but studies of candidate genes involved in ADHD etiology, which include specific catecholaminergic and serotonergic signaling proteins, have not been able to account for > 3–4% of the total variance in ADHD phenotype (Néale et al., 2010). Thus, it is possible that gene-environment interactions are inflicting the heritability estimates (Matthews et al., 2014).

Environmental factors also likely play a role in the development of ADHD. Fetal exposures to alcohol, cigarette smoke, and lead have been shown to be associated with development of ADHD and ADHD-symptoms in children and in animal models (Banerjee et al., 2007; Eubig et al., 2010; Abbott and Winzer-Serhan, 2012). More recently, exposure to bisphenol A (BPA) has been studied as a possible contributor to ADHD. BPA is widely used in plastics, epoxy resins (used to line cans and as dental sealants), food packaging and thermal receipts, and is also found in recycled paper products such as toilet paper (Michaelowicz, 2014). BPA, a known endocrine disruptor, interacts with several steroid receptors and has been shown to disrupt numerous physiological systems in animals (Vandenberg et al., 2013). Further, it has been linked to many adverse health effects in both adults and children (Rochester, 2013). In children, BPA has been implicated in neurobehavioral disruption in those exposed both prenatally and postnatally (Rochester, 2013; Braun et al., 2009; Perera et al., 2012; Maserejian et al., 2012; Casas et al., 2015) and ADHD-symptoms such as hyperactivity have been shown to be associated with exposure during development (Braun et al., 2009; Braun et al., 2011; Casas et al., 2015; Braun and Hauser, 2011; Harley et al., 2013). A preliminary search of the literature on environmental chemical exposures and ADHD symptoms in rodents found evidence for associations between BPA and ADHD-like symptoms (see Problem Formulation, below).

From a mechanistic standpoint, there is also ample evidence that BPA can contribute to ADHD. BPA has been shown to disrupt the catecholaminergic and serotonergic signaling systems, in vitro and in vivo (Komada et al., 2014; Ishido et al., 2004; Ishido et al., 2005; Ishido et al., 2007; Masuo et al., 2004a; Mizuo et al., 2004; Zhou et al., 2009; Tian et al., 2010; Honma et al., 2006; Matsuda et al., 2012; Miyatake et al., 2006; Yanagihara et al., 2005; Yoned et al., 2003; Toyohira et al., 2003; Itoh et al., 2012; Nakamura et al., 2010; Castro et al., 2013; Marquis and Haynes, 2010); these signaling systems are implicated in the manifestation of ADHD (Aguiria et al., 2010; Swanson et al., 2007; Wilens, 2008). Thus, the human and animal evidence, along with the mechanistic data, point to BPA as a possible environmental contributor to the development of ADHD. However, this connection has not previously been systematically reviewed.

The National Institute of Environmental Health Sciences, Office of Health Assessment and Translation (OHAT) developed a systematic review framework (Rooney et al., 2014) for environmental health research questions. The OHAT framework was adapted from well-established systematic review methods in clinical health research. It standardizes the review process by providing transparent procedures for collecting evidence, evaluating the validity of the study designs and methods, rating confidence in the body of evidence, and integrating human and animal evidence for a final health effect conclusion. OHAT has conducted a review utilizing this framework; a draft version is available online (National Toxicology Program, 2013). We developed a systematic review methodology, based on this framework.

In the present review, we explored the connection between early BPA exposure and the development of ADHD in humans, as is suggested by the human literature. The first step in a systematic review is to define the protocol through a Population-Exposure-Comparator-Outcome (PECO) statement (Table 1). Our review included literature in which rodents or humans were exposed prenatally (or early postnatally) to BPA, with control groups or low exposure groups included for comparison. Outcomes included hyperactivity symptoms, diagnoses or behaviors. Studies were experimental rodent studies, or epidemiological human studies. We analyzed the rodent studies through meta-analysis. Using the OHAT framework, we synthesized the human and animal evidence streams to arrive at a conclusion about the hazard early-life BPA exposure poses for hyperactivity in humans.

2. Methods

Our methodology was designed based on the OHAT framework detailed in Rooney et al. (Rooney et al., 2014) and the National Toxicology Program’s (NTP) Draft Protocol for Systematic Review to Evaluate the Evidence for an Association Between Bisphenol A (BPA) Exposure and Obesity, Appendix 2 (National Toxicology Program, 2013). Our protocol is available as Supplementary Information (Document 1), however, we did not publish or register the protocol prior to carrying out our review. We acknowledge this may be a limitation, as publication of systematic review protocols is recommended to promote transparency and reduce the potential for bias.

Briefly, the framework includes seven steps: 1) Problem Formulation and Protocol Development, 2) Search and Selection of Studies for Inclusion, 3) Data Extraction, 4) Assessment of Quality of Individual Studies, 5) Rating of Confidence in the Body of Evidence (including meta-analysis), 6) Translation of Confidence Rating to Evidence of Health Effects, and 7) Integration of Animal and Human Evidence for Hazard Identification Conclusions. Additionally, our analysis was completed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement checklist (see Supplementary Information Document 2) (Whaley et al., 2016).

2.1. Problem formulation and protocol development

This systematic review arose from an interest in neurodevelopmental disorders, and how they may be associated with chemicals in the environment. We started with a preliminary scoping review, prior to the methodology development, to determine which chemicals were associated with the development of ADHD in humans and animals. Many postnatal-onset, non-infectious diseases/disorders have unknown etiology and may be due to exposure to environmental factors in the womb (Dolinoy et al., 2007; Heindel and Vandenbergh, 2015).
Therefore, our focus was on early life exposure: gestational to three months old in humans, and the corresponding development in rodents (i.e., gestation to puberty). These exposure time-frames were determined based on Bayer et al., 1993, which uses neurological development to equate human and rodent developmental timelines (Bayer et al., 1993). For the animal studies, we focused on mice and rats, as they are the most widely used animal models in clinical studies, and several diseases and disorders have established mouse or rat models, including ADHD (Russell, 2011). Although other species (e.g., fish, insects) could have been included, we chose to focus on rodents as the most widely-used clinical models. From the initial scoping review, we identified many chemicals associated with ADHD in humans and rodents. We chose BPA for several reasons: the robust body of literature in humans and rodents, relevance to human health (i.e., current scientific interest in the health effects of BPA and the high potential for human exposure), and to highlight the relatively new idea that BPA may be contributing to ADHD. This led to our research question “Does early exposure to BPA contribute to the development of ADHD in humans?” We then formulated the Population, Exposure, Comparators, and Outcome (PECO) statement (Table 1), which included hyperactivity, among other endpoints related to ADHD. After our initial screening with this PECO statement (after endpoint identification but before data/outcome extraction), we further narrowed our question to “Does early life exposure to BPA contribute to postnatal hyperactivity?” to reduce the scope and increase the feasibility of our review, and included only the hyperactivity studies.

### Table 1
Population-Exposure-Comparator-Outcome (PECO) statement.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants/Population (observational or experimental studies)</strong></td>
<td><strong>Exposure</strong></td>
</tr>
<tr>
<td>• Humans</td>
<td>• Exposures to chemical mixtures in animals</td>
</tr>
<tr>
<td>• Rodents</td>
<td>• Exposures to mixtures in humans where specific BPA exposures were not identified</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td><strong>Comparators</strong></td>
</tr>
<tr>
<td>• Exposure to bisphenol A (BPA) during any time between conception to 3 months old in humans, and conception to puberty in rodents (postnatal day 35 in rats and 40 in mice)</td>
<td>• No determination of outcomes with respect to exposure level in humans</td>
</tr>
<tr>
<td>• Exposure to controlled doses of BPA via an exposure method (e.g. diet, injection, drinking water, gavage)</td>
<td>• No controls in experimental studies</td>
</tr>
<tr>
<td>• Exposure to environmental exposures measured via biological samples of mothers during gestation and neonates after gestation.</td>
<td>• All other non-ADHD physiological effects</td>
</tr>
<tr>
<td>• Exposures measured via environmental monitoring, occupational exposures (i.e. surveys)</td>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td><strong>Publication parameters</strong></td>
</tr>
<tr>
<td>• Low exposure quartiles (observational studies)</td>
<td>• Peer-reviewed</td>
</tr>
<tr>
<td>• Vehicle-only treatment controls (experimental studies)</td>
<td>• Original data</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>• Studies must be published in English</td>
</tr>
<tr>
<td>• Diagnosis of ADHD or any related symptoms (humans)</td>
<td><strong>Inclusion criteria</strong> Exclusion criteria</td>
</tr>
<tr>
<td>• Determination of activity levels or other ADHD symptoms via any methodology (e.g. questionnaires for humans, observation for humans/animals)</td>
<td>• All non-human primates and non-rodent animals and organisms, including wildlife, aquatic species, and plants</td>
</tr>
<tr>
<td><strong>Publication parameters</strong></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>• Peer-reviewed</td>
<td>• Exposures to chemical mixtures in animals</td>
</tr>
<tr>
<td>• Original data</td>
<td>• Exposures to mixtures in humans where specific BPA exposures were not identified</td>
</tr>
<tr>
<td>• Studies must be published in English</td>
<td><strong>Exclusion criteria</strong></td>
</tr>
</tbody>
</table>

### Table 2
ADHD and BPA search logic.

<table>
<thead>
<tr>
<th>Disorder and symptom search</th>
<th>Search logic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(bisphenol-A OR BPA) AND (ADHD OR attention-deficit OR inattention OR inattentiveness OR sustained-attention OR disruptive-behavior OR habituation OR hyperactivity OR overactivity OR hyperactive OR overactive OR impulsivity OR impulsive OR impulse-control OR impulsivity OR delay-of-reinforcement OR delayed-reinforcement OR motor-control OR motor-activity OR disinhibition OR inhibition)</td>
<td></td>
</tr>
</tbody>
</table>

* The search logic was identical for PubMed, Web of Science, and Toxline.

A comprehensive literature search was performed in order to identify studies describing the effects of early life exposure to BPA on ADHD-related behaviors. Experts were consulted for search criteria inclusion (see Table 2 for search terms). The search included all articles published and indexed for all literature up to January 1, 2017 that were in the English language. Electronic searches were performed in PubMed, Web of Science, and Toxline. Two reviewers (AB, JR) screened all titles and abstracts independently, using the software Distiller SR® (Evidence Partners, Ottawa, Ontario, Canada (Evidence Partners)). For inclusion in the systematic review, the studies had to contain original data, be in the English language, include some measure of BPA exposure, and assess if BPA exposure affected the development of ADHD or associated behaviors in mice, rats or humans (e.g., hyperactivity, impulsivity, and inattention). Exposure to BPA had to occur at < 3 months for humans, up to postnatal day 35 for rats and up to postnatal day 40 for mice, either gestational (via maternal exposure) or directly to the offspring. The PECO statement, governing which studies were included/excluded, is presented in Table 1. The two reviewers reconciled study inclusion conflicts or discrepancies through discussion. Fig. 1 shows reasons for full text exclusions (a detailed list of included/excluded studies and reasons for exclusion is available upon author request). We did not hand search the reference lists of included papers. After determining relevant endpoints and selecting studies for full review, but before data and outcome extraction, the specific ADHD symptom “hyperactivity” was chosen.

### 2.2. Search and selection of studies for inclusion

A comprehensive literature search was performed in order to identify studies describing the effects of early life exposure to BPA on ADHD-related behaviors. Experts were consulted for search criteria inclusion (see Table 2 for search terms). The search included all articles published and indexed for all literature up to January 1, 2017 that were in the English language. Electronic searches were performed in PubMed, Web of Science, and Toxline. Two reviewers (AB, JR) screened all titles and abstracts independently, using the software Distiller SR® (Evidence Partners, Ottawa, Ontario, Canada (Evidence Partners)). For inclusion in the systematic review, the studies had to contain original data, be in the English language, include some measure of BPA exposure, and assess if BPA exposure affected the development of ADHD or associated behaviors in mice, rats or humans (e.g., hyperactivity, impulsivity, and inattention). Exposure to BPA had to occur at < 3 months for humans, up to postnatal day 35 for rats and up to postnatal day 40 for mice, either gestational (via maternal exposure) or directly to the offspring. The PECO statement, governing which studies were included/excluded, is presented in Table 1. The two reviewers reconciled study inclusion conflicts or discrepancies through discussion. Fig. 1 shows reasons for full text exclusions (a detailed list of included/excluded studies and reasons for exclusion is available upon author request). We did not hand search the reference lists of included papers. After determining relevant endpoints and selecting studies for full review, but before data and outcome extraction, the specific ADHD symptom “hyperactivity” was chosen.

### 2.3. Data extraction

Included studies were data-extracted by one reviewer (JR) and then quality checked by an independent reviewer (AB). The data included were: author information, year of publication, animal model and strain, dose level, age, route of exposure, dosing regimen, age when measurements of hyperactivity were assessed, specific type of activity, sample size, and measurements of activity (i.e., mean, standard deviation, and standard error). Measures of hyperactivity in rodents included total activity, total horizontal activity, spontaneous motor activity,
distance travelled, and the number of line crosses. In humans, Behavior Assessment System for Children, Second Edition (BASC-2) scores, Conner's ADHD/DSM-IV (CADS), ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders-4th Edition (ADHD-DSM-IV), and the Conner's Parent Rating (CPRS) scales specifically assessing hyperactivity were included. Data were extracted from figures or graphs using the Universal Desktop Ruler® (AVPSoft.com) software as needed, with measurements taken in triplicate by a single reviewer and quality checked for accuracy by a second reviewer. Authors were contacted by email if pertinent data was not reported, with one follow-up request if we received no response.

2.4. Assessment of the quality of individual studies

Briefly, risk of bias of experimental methodology was assessed by answering the 14 animal questions and the 11 human questions in the OHAT Risk of Bias Tool (see Table 3 in the NTP BPA Draft Protocol (National Toxicology Program, 2013)). The risk of bias questions used in this analysis covered biases in: selection of subjects, performance of implementing methodology, accounting for confounding variables, attrition/exclusion of subjects, detection/outcome assessment (including quality of exposure assessment), selective reporting of outcomes, and statistical methodology (see Supplementary Information Document 3 for details). Questions were answered using the following ratings: “definitely low risk of bias,” “probably low risk of bias,” “probably high risk of bias,” “definitely high risk of bias,” or “not reported” based on standardized responses. Two reviewers (JR, AB) assessed each study independently and discrepancies were resolved through discussion. Contact with authors was attempted up to two times by email if risk of bias information was not reported.

The ratings of individual answers were then combined and used to tier the studies according to study confidence (i.e., high, moderate, or low). This tiering system is used to remove individual studies with low confidence. These are studies that have many components of high risk of bias in their experimental designs, which may lead to bias in the study results. (see Supplementary Information Document 4 and OHAT 2015 Handbook for a detailed explanation of the tiering process (National Toxicology Program, 2015)).

2.5. Rating confidence in the body of evidence

In this step, we analyzed the pertinent studies in each data stream (i.e., animal and human), which yielded an animal body of evidence and a human body of evidence. For the animal evidence, only the studies used in the meta-analysis were included (as discussed below in “Meta-Analysis”). The overall confidence in each body of evidence was
characteristics of animal and human studies assessed in this review.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies total</td>
<td>29</td>
</tr>
<tr>
<td>Mean sample size</td>
<td>13.2, range 3-30</td>
</tr>
<tr>
<td>2016-2010</td>
<td>17 (59)</td>
</tr>
<tr>
<td>2009-2000</td>
<td>11 (38)</td>
</tr>
<tr>
<td>1999-1990</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Sex</td>
<td>Sex</td>
</tr>
<tr>
<td>Both</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Females only</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Males only</td>
<td>10 (35)</td>
</tr>
<tr>
<td>Doses assessed (µg/kg/day)</td>
<td>Number (%) of studies with doses within each range</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>1 (3)</td>
</tr>
<tr>
<td>1-10</td>
<td>6 (21)</td>
</tr>
<tr>
<td>11-100</td>
<td>17 (59)</td>
</tr>
<tr>
<td>101-1000</td>
<td>12 (41)</td>
</tr>
<tr>
<td>1001-10,000</td>
<td>11 (38)</td>
</tr>
<tr>
<td>&gt; 10,000</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Age of exposure</td>
<td>Age of Exposure</td>
</tr>
<tr>
<td>Gestational only</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Gestational and prepubertal</td>
<td>17 (59)</td>
</tr>
<tr>
<td>Prepubertal only</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Age of outcome measurement</td>
<td>Age of outcome measurement</td>
</tr>
<tr>
<td>After puberty</td>
<td>19 (66)</td>
</tr>
<tr>
<td>Before puberty</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Both</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Measure of hyperactivity</td>
<td>Measure of hyperactivity</td>
</tr>
<tr>
<td>Horizontal activity</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Total activity</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Animal model</td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Rat</td>
<td>18 (62)</td>
</tr>
</tbody>
</table>


evaluated. First, initial confidence in each of the bodies of evidence was determined by evaluating the following key study design features: controlled exposure, exposure prior to the assessment of the outcome, outcome data that was collected at the individual level, and use of comparison groups. The confidence scale was rated from “high confidence” to “very low confidence,” where “high confidence” has all four features, “moderate confidence,” three features, “low confidence,” two features, and “very low confidence,” one or less features. A well-conducted experimental study will have all four features and thus start out with high initial confidence. Most human epidemiological cohort studies will have three factors (all but controlled exposure) and start out at moderate initial confidence.

After the initial confidence rating was determined, factors that increased or decreased confidence in the body of evidence were considered using a method adapted from the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Balshem et al., 2011). The body of evidence was evaluated for downgrading using the following factors: severity of risk of bias, unexplained inconsistency, indirectness with respect to animal models/routes of exposure, imprecision of the effect size, and publication bias. Next, upgrading factors were assessed that potentially increase confidence in the body of evidence: large magnitude of effect, results showing presence of dose-response (e.g., linear or non-linear), residual confounding (e.g., bias towards the null), consistency across different models and population types, and any other relevant experimental features (e.g., rare outcomes). Decreasing and increasing factors each had the potential to change the confidence in the body of evidence by up to two levels. Finally, the initial confidence, decreasing factors, and increasing factors were summed, generating the confidence in the body of evidence rating, which is scaled from “high” to “very low.”

2.6. Meta-analysis

Meta-analysis was used to determine if BPA administration resulted in hyperactive behaviors. For this analysis, only animal studies were assessed because the body of literature had conflicting results that could be evaluated using meta-analytical techniques. Meta-analysis of environmental studies can be difficult, due to the wide range of doses (as compared to clinical studies which often include only one or two doses). Although there are several techniques to address this issue (e.g., pooling doses, splitting the control Ns, choosing one dose, etc.), we decided that choosing one dose would introduce the least amount of bias and heterogeneity. We chose 20 µg/kg/day because it was the dose with the most information (studies), below the EPA’s established tolerable daily intake (TDI) of 50 µg/kg/day. Thus, any information acquired from this dose would indicate effects below the TDI, and would be useful for new studies and/or risk assessments. We expanded the doses included to range 15–25 µg/kg/day to account for dosing margin of error, as per the advice of an expert in the field. Studies that did not encompass these doses were not included in the meta-analysis. Further, only the studies used in the meta-analysis were analyzed for the other parameters rating the confidence in the body of evidence (such as publication bias, imprecision, risk of bias, etc.). The outcomes were continuous for all experiments and were expressed as means, standard deviations, and sample sizes. All data from the experiments were analyzed using a random effects model, as it was assumed a priori that the studies differed for reasons beyond sampling error, therefore our set of studies represented a distribution of true effects (Borenstein et al., 2011). All analyses were performed using Comprehensive Meta-Analysis Version 3 * software (Biostat, Englewood, New Jersey, USA) and summary effect sizes were expressed using Hedge’s g (g), the unbiased estimate of Cohen’s d (i.e., the standardized mean difference) (Borenstein et al., 2011; Vesterinen et al., 2014). Statistical significance was accepted at p < 0.05. Because of the evidence that ADHD/hyperactivity is present at different rates in boys and girls (Aguirar et al., 2010), we decided, a priori, to include a subgroup analysis with respect to sex. We also ran confirmatory analysis to see if there were differences between 15, 20, and 25 µg/kg/day. Publication bias was evaluated quantitatively using an Egger’s test. A qualitative analysis of the remaining animal studies (significance and direction of effects) is
presented in Supplementary Information Document 6. These studies were not included in determining the confidence in the body of evidence.

2.7. Translation of confidence rating to evidence of health effects

Human and animal evidence streams were assessed separately. Confidence in the body of evidence was combined with evidence of an effect (assessed either through the meta-analysis [animal] or qualitatively [human]) to determine whether the body of evidence supported an association between exposure to BPA and hyperactivity. If the body of evidence shows evidence of an effect, the confidence rating translates directly to an evidence rating of “high,” “moderate,” or “low,” but “very low” translates to “inadequate” level of evidence for the health effect. In the OHAT framework, if there are no effects seen in the body of evidence, a “high” confidence in the body of evidence translates to “evidence of no effect,” while “moderate,” “low,” or “very low” confidence in the body of evidence translates to “inadequate” evidence (National Toxicology Program, 2015).

2.8. Integration of animal and human evidence for hazard identification conclusions

In the final step, human and animal evidence ratings were integrated to determine the final hazard identification conclusion. The hazard identification can then be used in the context of risk assessment to make further recommendations (National Toxicology Program, 2015). The OHAT framework has five possible hazard identification conclusions: 1) known to be a hazard to humans, 2) presumed to be a hazard to humans, 3) suspected to be a hazard to humans, 4) not classifiable as a hazard to humans, and 5) not identified to be a hazard to humans. These categories are similar to hazard classification labels of other organizations (National Toxicology Program, 2015). If there were to be no literature for a particular data stream (e.g., animal or human), the evidence for that data stream is determined to be “inadequate,” and the conclusion is based on the existing evidence.

3. Results

3.1. Literature search, screening, and data extraction

Study selection is summarized in a flow diagram (Fig. 1). Literature searches in PubMed identified 463 potentially relevant studies; Web of Science, 966; and Toxline, 118. After removing duplicate records, the screening of 913 records using inclusion criteria identified a total of 29 rodent (Komada et al., 2014; Ishido et al., 2004, Ishido et al., 2005, Ishido et al., 2007, Ishido et al., 2011; Masuo et al., 2004a,b; Tian et al., 2010; Matsuda et al., 2012; Adriani et al., 2003; Anderson et al., 2013; Ferguson et al., 2012; Kiguchi et al., 2007, Kiguchi et al., 2008; Negishi et al., 2004; Wolstenholme et al., 2013; Zhou et al., 2011; Farabollini et al., 1999; Stump et al., 2010; Xu et al., 2007; Nakamura et al., 2012; Nago et al., 2014; Negishi et al., 2003a,b; van Esterik et al., 2014; Kundakovic et al., 2013; Hass et al., 2016; Heredia et al., 2016; Hicks et al., 2016; Rebuli et al., 2015) and three human (Casas et al., 2015; Braun et al., 2011; Harley et al., 2013) studies as relevant. The 29 rodent studies encompassed doses from 0.25 to 50,000 μg BPA/kg/day. For the meta-analysis, we included only doses from 15 to 25 μg BPA/kg/day, which included 12 studies and 25 independent effects. Table 3 shows the summarized characteristics of the studies. In the included animal studies, hyperactivity was tested in several different apparatus, including open field boxes, experimental cages, holeboards, tilt cages, and scales. The methods used to assess hyperactivity included infrared photobeam technology, video and computer-based tracking systems, video and manual recording, live manual recording, tilt-switches, and movement on a scale (measured in changes in grams) (Komada et al., 2014; Ishido et al., 2004, Ishido et al., 2005, Ishido et al., 2007, Ishido et al., 2011; Masuo et al., 2004a,b; Tian et al., 2010; Matsuda et al., 2012; Adriani et al., 2003; Anderson et al., 2013; Ferguson et al., 2012; Kiguchi et al., 2007, Kiguchi et al., 2008; Negishi et al., 2003a,b; Negishi et al., 2004; Wolstenholme et al., 2013; Zhou et al., 2011; Farabollini et al., 1999; Stump et al., 2010; Xu et al., 2007; Nakamura et al., 2012; Nago et al., 2014; van Esterik et al., 2014; Kundakovic et al., 2013; Hass et al., 2016; Heredia et al., 2016; Hicks et al., 2016; Rebuli et al., 2015). The human measures of hyperactivity were assessed using the BASC-2, CADS, ADHD-DSM-IV, and Conner’s Parent Rating scales (Casas et al., 2015; Braun et al., 2011; Harley et al., 2013).

3.2. Individual study quality

The risk of bias results are presented in Fig. 2 and Supplementary Information Document 4. All the studies had either high (tier 1) or moderate (tier 2) confidence, so none of them were removed from analysis (see Supplementary Information Document 4 (National Toxicology Program, 2015)). Only the studies analyzed in the meta-analysis are presented in Fig. 2. Supplementary Information Document 4 presents the risk of bias data for all studies.

For an overall picture of risk of bias, the individual risk of bias ratings were pooled by type of bias: Selection, Confounding, Performance, Attrition/Exclusion, Detection/Outcome, Reporting, and Statistical (Fig. 2). Studies were that were rated “−−” (indicated by
yellow) were “probably high” in their risk of bias ratings, OR had parameters where the answers were not reported by the study authors.

In general, the animal studies performed well in the areas of Detection/Outcome bias, and Reporting bias, indicating that they had low risk of bias in these areas. The Attrition/Exclusion bias was slightly higher, with more studies having a “probably high” risk of bias, and the Performance bias was even higher, with a few studies having “definitely high” risk of bias. Areas with the highest risks of bias included Selection, Confounding, and Statistical. These included areas such as blinding, allocation concealment, accounting for confounding factors, and the data passing statistical assumptions. It should be noted that if the authors do not report a parameter, it was not known if these parameters represent true risks of bias or failure of the authors to report the parameter.

The quality of the human studies was high: all of studies (Casas et al., 2015; Braun et al., 2011; Harley et al., 2013) identified and controlled for relevant covariates, applied well-established methods to measure the outcome, and utilized valid methods that allowed for the quantification of BPA in study subjects (according to our methodology, adapted from the OHAT BPA Draft Protocol (National Toxicology Program, 2013), see SI S2 Document). Two of the studies did not use acceptable methods to measure covariates, and were rated “probably high risk” for that individual parameter (see Fig. 2 for details) (Casas et al., 2015; Harley et al., 2013).

Since all the studies received either high or moderate ratings, no studies were removed from the review. The answers and ratings of the individual questions, as well as the tiering scores, are presented in Supplementary Information Document 4.

3.3. Rating confidence in the body of evidence

3.3.1. Determination of effect

We determined the effect in the human studies qualitatively by looking at the effects reported in the primary studies and comparing them overall. All three studies showed effects, but this differed by sex, time of assessments, time of exposure (i.e., prenatal vs. postnatal exposure), and who did the assessments (i.e., teacher vs. parents). In Braun et al., prenatal BPA exposure was positively associated with hyperactivity scores in 3-year-old girls (Braun et al., 2011). Casas et al. found prenatal BPA to be associated with increased teacher-reported hyperactivity in 4-year-old boys, but not in girls. Interestingly, at 7 years old, hyperactivity was decreased in girls with respect to BPA exposure, but this association was not significant (Casas et al., 2015).

Lastly, Harley et al. did not find associations with prenatal BPA exposure. They did find that childhood BPA exposure was associated with increased teacher-reported hyperactivity at age 7 in girls (Harley et al., 2013), although these data were not included in our analysis, as we limited our analysis to prenatal/early post-natal exposures. It should be noted that there were differences in the populations studied, such as time of assessment. Because of this, we determined that the studies were too different from each other to be compared in using meta-analysis. For the animal literature, we conducted a meta-analysis to rectify differences between studies with positive, negative, and no effects. The meta-analysis included doses of 15, 20, and 25 μg/kg/day, which accounted for 12 of the 29 animal studies and included 25 independent measures of hyperactivity. The three doses did not differ significantly \( p < 0.993 \) and thus were combined for all subsequent analyses. The Supplementary Information Document 5 contains summary statistics including the standard mean difference and confidence intervals of each study.

The forest plots (Figs. 3 and 4) show the individual effects of each study, and the overall meta-values. When males and females were analyzed together, BPA exposure did not significantly impact hyperactivity \( g = 0.088, 95\% CI = -0.057–0.232, p = 0.237; \) Fig. 4). However, when males were analyzed separately, there was a significant increase in hyperactive behaviors with BPA exposure among males \( g = 0.243, 95\% CI 0.038–0.448, p = 0.020; \) Fig. 4).

Due to observational evidence in humans suggesting a higher prevalence of ADHD in males, we completed an evaluation assessing differences between sexes. There were 12 and 13 data points for females and males, respectively. This analysis showed that the males differed significantly from females \( p < 0.035 \). Heterogeneity of the data was calculated using \( I^2 \) (the distribution of effect sizes). This analysis indicates percentage of total variation across studies is due to heterogeneity rather than chance (Higgins et al., 2003). Our analysis did not show a significant difference between studies overall with a very low \( I^2 \) value \( (I^2 = 5.042, \ p < 0.391) \), meaning that the differences in effect sizes due to variables besides BPA treatment were small. Because the \( I^2 \) value was so low \( (\sim 5\% \ \text{heterogeneity}) \), we did not pursue sub-group analysis or meta-regression, as this would not have added to the data for the purposes of hazard identification.

3.3.2. Publication bias

An Egger’s Test analysis using the standard mean differences (SMDs) was non-significant \( (p = 0.33997, 2-tailed) \), indicating publication bias is unlikely. It has been shown that using SMDs to determine publication bias can over-estimate asymmetry, leading to false-positive results (Zwetsloot et al., 2017). Since we did not find significant positive effects, there was no danger of having a false-positive, so we did not conduct further analysis (for example by plotting the SMD against a sample size-based precision estimate).

3.3.3. Confidence in the body of evidence

The meta-analysis animal studies (12) and all the human studies (3) were included in the analysis of the confidence in the body of evidence. For the animal studies, the initial confidence in the body of evidence was high \((++++)\) due to the fact that all the studies had controlled exposures, exposures prior to outcomes, individual outcome data, and control/comparison groups (Macleod et al., 2008). The risk of bias was determined for all the studies identified. Although there were more high-quality studies than moderate quality studies, indicating the risk of bias should not be downgraded \((++++)\), presented a substantial risk of bias, and thus we downgraded the body of evidence one level. Other downgradable factors (indirectness, imprecision, unexplained inconsistency, and publication bias) were acceptable and did not warrant a downgrade. Because these factors were determined by meta-analysis, only the studies used in the meta-analysis were included for these assessments. Specifically, no imprecision was found, via methods outlined in the OHAT Handbook (National Toxicology Program, 2015, page 59). No unexplained inconsistency was found using \( I^2 \) statistics \((0–40\%, \ \text{judged as “might not be important”}) \) (National Toxicology Program, 2015, page 54). Similarly, quantitative analysis of the publication bias determined no bias. The animal body of evidence was upgraded once due to plausible dose-responses. This was because, across the entire animal body of evidence, all the male significant effects showed a linear dose-response. The methodology and data for this analysis is presented in Supplementary Document 7. No other factors (large magnitude of effect, residual confounding, consistency, or other factors) warranted an upgrade. Thus, the final rating for the animal body of evidence was “high” \((++++)\), Fig. 5).

For the human studies, we qualitatively assessed the body of evidence. The body of evidence was initially rated as moderate \((+++)\) because of the following positive characteristics: outcomes prior to exposure, individual outcome data, and comparison groups \((i.e., \ \text{lowest quartile groups})\). Epidemiological studies inherently do not have controlled exposures, thus the body of evidence could not receive the highest rating. The human body of evidence was downgraded once for having unexplained inconsistency \((due \text{ to the fact that there were different outcomes, based on age, sex, and outcome assessment})\). The body
of evidence was upgraded once for dose-response curves across all studies that supported the plausible biological effects of BPA. Because BPA has been shown to illicit both non-monotonic and monotonic (i.e., non-linear and linear) dose-response curves in a wide variety of organisms (Vandenberg, 2014), we accepted both types of curves as a basis for upgrading. To determine if a dose response was present, all the effects were standardized, pooled, and dose-response was examined across the entire human body of literature (rather than in each individual study) for two age groups (3–4 year olds and 7 year olds), and for each sex. The methodology and data are presented in Supplemental Document 8. For the 3–4 year olds, there was a "U" shaped (or possibly positive linear) response in girls, and for the boys there appeared to be an inverted "U" shaped response. While there was no significant effect in girls at 7 years old with prenatal exposures, there was a trend of decreasing hyperactivity (Harley et al., 2013). Interestingly, we found that there was a decreased linear dose-response across all studies (which assessed them) in girls at 7 years old. Thus, the final confidence rating for the human body of evidence was "moderate" (+++, Fig. 6).

3.4. Translation of confidence rating to evidence of health effects

The meta-analysis for the animal body of evidence showed a significant effect for males. Therefore, the "high" confidence rating derived in Step 5 for the animal body of evidence was translated to a "high" level of evidence for hyperactivity. The human body of evidence showed significant effects in all three studies, although these effects differed by age and sex (Casas et al., 2015; Braun et al., 2011; Harley et al., 2013). Therefore, the "moderate" confidence rating from the human body of evidence was translated to a "moderate" level of evidence for hyperactivity.

3.5. Hazard identification

The hazard identification was determined by integrating the human and animal ratings for evidence of health effects from the previous step, as shown in Fig. 7. The final rating identified BPA as a "presumed" hazard to human health with regard to hyperactivity.

4. Discussion

Our systematic review found that early BPA exposure is associated with a presumed hazard of hyperactivity in humans. Our conclusion is based on "moderate" levels of evidence for the human and "high" levels of evidence for animal literature. The systematic review included all the available literature up to January 1, 2017; 29 animal studies, and three human studies. A meta-analysis of studies in animals showed increased hyperactivity with early life exposure to BPA in males. In humans, all three studies showed significant effects of BPA on increased hyperactivity with early life exposure to BPA in males. In humans, all three studies showed significant effects of BPA on increased hyperactivity, although there were differences in the sexes and windows of exposure. These results, along with a qualitative and quantitative analysis of the entire human and rodent bodies of literature (e.g., risk of bias, publication bias, dose-response, etc.) were quantitatively...
Fig. 4. Male vs. female hyperactivity using a random effects model. Each circle and whisker represents the effect size and 95% confidence interval for the study, and the size of the circle indicates the relative weight of the study in the calculation of the meta-value. The diamond represents the meta-value and the 95% confidence intervals. F: female; M: male; A: adult; J: juvenile; B: both sexes.

Fig. 5. Confidence in the body of evidence evaluation for animal studies. + indicates an upgrade in the confidence in the body of evidence; − indicates a downgrade in the confidence in the body of evidence. Summation of the "+5" and "−5" in each column equals the number in the bottom row. Summation of the "+5" in the bottom row results in the final rating in the bottom right-hand box.
integrated to arrive at the final hazard identification conclusion.

This review also identified several interesting outcomes and ideas for further research. These, along with a discussion of the strength and limitations of the review and possible modes of action of BPA on neurodevelopment, are examined below.

4.1. Sex

In our analysis, BPA showed a significant effect on male, but not female, rodent hyperactivity. However, it should be noted that we did not account for any other confounders in our analysis, so it is possible these differences were due to other factors. Interestingly, the human results in our review showed mixed outcomes: some had a larger effect in girls, and some in boys. These results, however, did not change our hazard identification conclusion, as the goal is to identify and protect the most sensitive populations, and both males and females are exposed in the general population. Because of this, any effect, regardless of sex or other possible variants to the population, is considered in the "Evidence of Health Effect" step of this methodology.

In the human population, ADHD is more prevalent in boys than girls (Aguiar et al., 2010), with the caveat that referral bias appears to cause the under-diagnosis of ADHD in girls (Gershon, 2002). Further, subtype distributions appear to change in adulthood; studies indicate women are diagnosed with the combined subtype more frequently than men and suffer greater impairment on several measures of ADHD symptoms (Robison et al., 2008; Rucklidge, 2010).

It is common for effects to vary across sexes (Palanza and Gioiosa, 2008), particularly with endocrine disrupting chemicals, although the
exact mechanisms are often unclear. However, these sex differences do suggest an endocrine basis for the differences in effects seen in these studies. Interestingly, a recent study found that being born with hypospadias, a disorder of the penis caused by disrupted steroids before birth, was associated with increased likelihood of having ADHD and other neurodevelopmental disorders (Butwicka et al., 2015). In two of the human studies in the present analysis, early BPA exposure was associated with hyperactivity in girls, but not boys (Braun et al., 2011; Harley et al., 2013). In one study, hyperactivity in girls at age 7 was correlated with BPA exposure at 5 years of age but not gestational exposure (Harley et al., 2013). In contrast, the other human study showed that gestational exposure to BPA was correlated with hyperactivity in girls, while childhood exposure (i.e., 1–3 years of age) was not (Braun et al., 2011). A third study showed increased hyperactivity in boys, but not girls, which attenuated with age (Casas et al., 2015). Additional studies could be done to understand the role of sex and windows of susceptibility with respect to hyperactive behaviors. These include a focus on female rodent data, which is lacking, as well as comparisons in rodents between different time periods of exposure during gestation and postnatally (i.e., early gestation vs. late gestation vs. postnatal exposures). Another interesting research avenue that has not been well-studied is whether levels of hyperactivity change as rodents age (as they appear to do in humans). Although studies such as these would help to further understand the gene-environment interaction of the development of this disorder, the current body of evidence points to BPA exposure contributing to hyperactivity, and research resources should be carefully allotted for maximum protection of human health.

4.2. Dose and dose response

We chose to conduct a meta-analysis of the 20 μg/kg/day dose, because that was the most frequently studied dose in the body of evidence below the established TDI of 50 μg/kg/day. We included 15–25 μg/kg/day in order to account for dosing margin of error within the studies (an analysis of these doses (Willcutt et al., 2005; Franke et al., 2009; Vandenberg et al., 2013) showed no differences between doses). Because we found effects at 20 μg/kg/day, regulators should reconsider the acceptable “safe” level for BPA exposure in humans, as has been previously suggested (Vandenberg et al., 2012), and new risk assessments of sensitive endpoints (such as neurodevelopment) should be considered. In the rodent studies, significant meta-effects were seen in the males, but not in the females. When examining the male studies across the body of evidence, all the studies that showed individual positive significant effects also showed a linear dose-response, with increasing doses resulting in increased hyperactivity. In humans, there was also a dose response when all the studies were examined together; however, it appeared to be an inverted “U-shaped” (non-monicotonic) response in boys, and a “U-shaped” (or positive linear) response in girls. Non-linear dose-response curves are common in low-dose and endocrine mediated toxicity (Vandenberg et al., 2013) and it would not be surprising if dose responses differed across sexes, especially if one sex was more susceptible than the other. According to current US risk assessment protocols, a thorough dose-response analysis and exposure assessment, including an exploration of the sex differences, timing of exposure and assessment, and other sources of heterogeneity, would be the next steps toward full understanding of the neurodevelopmental risks posed by early life exposure to BPA.

5. Strengths and limitations of systematic review

We chose to base our methodology on the OHAT framework, in part, because of its usefulness in integrating several data streams (i.e., in vitro, in vivo, and human) even if one or more of the data streams has few (or no) studies. Often, there is little human data available, particularly in the environmental toxicology/health fields, due to the time and expense of conducting epidemiological studies and the ethical barriers for human controlled trials that involve human exposure to potentially hazardous chemicals. Thus, it is important to have methods for using animal data to inform human health hazard conclusions; indeed, animal models are traditionally used to study human health (de Vries et al., 2014).

Additionally, one of the strengths of this framework is that it can adjust for potential flaws (such as increased risk of bias in the methodologies), to allow conclusions to be drawn based on the available literature. Another strength is that these potential deficits and data gaps can be identified in order promote research that will strengthen the body of evidence in the most effective manner.

A possible limitation of the current systematic review was the exclusion of some data and some literature. All non-English papers were excluded from the search a priori due to a lack of resources for translating services. The meta-analysis of the animal studies was based on only doses ranging from 15 to 25 μg/kg/day, in order to reduce heterogeneity. Because of this limitation, we recommend additional risk assessment/dose analysis for BPA with regard to this endpoint.

Our analysis was also potentially limited by the inability to differentiate between actual bias and the failure of authors to report how they handled the methodological parameters evaluated in the systematic review (e.g., blinding, randomization, statistical assumptions). The risk of bias for the animal literature was generally low, except for in certain domains, including Selection, Confounding, and Statistical (Fig. 2). Most deficits were in the areas of randomization, controlling for confounding variables, unintended endocrine-disruptive exposures (i.e., phytoestrogens from rodent chow or BPA from housing), lack of binding of subjective measures (i.e., behavior), and statistical deficits (i.e., not testing for ANOVA [analysis of variance] assumptions). Better ratings of any or all of these risk of bias parameters would have allowed for a stronger confidence in the animal body of evidence (see Fig. 2 and Supplementary Information Document). That is, if a methodological step or question was not clearly reported in the study, it was rated “probably high” risk of bias (e.g., “there is insufficient information provided about how subjects were allocated to study groups”). For example, many of the statistical problems were due to the fact that the researchers did not report whether or not they tested for assumptions when carrying out their ANOVA analyses, and did not respond to inquiry. In total, all the rodent studies (29) were lacking the reporting of one or more risk of bias parameters. Authors were contacted up to two times, but responses were received for only 59% of the studies. Because of the difficulty of contacting authors, authors should follow thorough reporting guidelines, such as the ARRIVE guidelines (Kilkenny et al., 2010), and should include reporting of all risk of bias parameters. Further, peer-reviewers should insist that these elements be reported clearly in submitted manuscripts. For a list of risk of bias parameters that should be addressed in publications, see the Risk of Bias Tool (SI S2 Document), and for clarification of the questions, see the OHAT framework (Rooney et al., 2014; National Toxicology Program, 2015) and the PRISMA checklist (SI S1 Document).

6. Mechanisms

In the OHAT systematic review framework, in vitro (and in vivo mechanistic) studies are utilized as support for the in vivo human and animal data. This information can have important implications for the final hazard identification rating (Rooney et al., 2014). In the case of this systematic review, there are no strongly established mechanisms for ADHD or hyperactivity (Aguirai et al., 2010), and it would be unfounded to use the current in vitro literature to modify our final hazard rating. However, although BPA has been traditionally thought of as disrupting the estrogen signaling system (Rubin, 2011), there is a large body of literature linking BPA exposure to changes in the catecholaminergic and serotonergic signaling systems, which are suspected to be associated with ADHD etiology (Aguirai et al., 2010; Swanson et al., 2007; Wilens, 2008). While an extensive review of this topic is beyond
the scope of this paper, we have included a short overview of BPA’s effects on the development of catecholaminergic and serotoninergic regions of the brain relevant to ADHD.

ADHD has been associated with neurological dysfunction in humans, particularly in the prefrontal cortex, caudate nucleus, cerebellum, and corpus callosum. Catecholaminergic and serotoninergic systems have also been implicated in the mechanism of ADHD (Aguiar et al., 2010; Wilens, 2008). Dopamine, norepinephrine, and their transporters are important signaling molecules in the prefrontal cortex, and in the case of dopamine and dopamine transporter, the striatum. Disruptions in both of these brain areas are associated with ADHD (Aguiar et al., 2010), as well as disruptions in dopamine signaling, disrupted dopaminergic circuitry, and increased dopamine transporter (which reduces dopamine in the synapses). Stimulant drugs used to treat ADHD symptoms work to block dopamine transporter, and thus increase dopamine levels in the synapses (Swanson et al., 2007; Wilens, 2008).

Serotonin (5-HT) signaling has also been implicated in the etiology of ADHD, although its contribution to the disorder is not as well characterized. Neuroimaging studies have found that 5-HT transporter (SERT) activity is altered in ADHD patients, and there may be altered synthesis of 5-HT in ADHD (Oades, 2008). Further, interactions of dopamine and 5-HT appear to be important in regards to hyperactivity. In a knock-out dopamine transporter mouse model, drugs that modulated 5-HT and SERT activities were shown to reduce hyper-locomotion (Gainetdinov et al., 1999). Some amphetamine-type stimulants used to treat ADHD also modulate serotonin activity, although it is thought that the therapeutic action of these drugs is not due to changes in extra-cellular 5-HT (Solanto et al., 2001).

Many studies have shown that BPA causes disruptions to the dopaminergic system in animals, generally downregulating the system (Komada et al., 2014; Ishido et al., 2004; Ishido et al., 2005; Masuo et al., 2004a; Mizuo et al., 2004; Zhou et al., 2009; Ishido et al., 2007; Tian et al., 2010; Honma et al., 2006; Matsuda et al., 2012). In vitro evidence also supports increased catecholaminergic activity with BPA treatment (Miyatake et al., 2006; Yanaghara et al., 2005; Yoneda et al., 2003), and BPA may inhibit norepinephrine transporter (Toyohira et al., 2003). BPA exposure has also been shown to alter the serotoninergic system in vivo, generally appearing to upregulate activity. BPA exposure in rodents increased serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Honma et al., 2006; Itoh et al., 2012; Nakamura et al., 2010). Adult rats exposed to BPA also showed increased tryptophan hydroxylase 2 activity, the rate-limiting enzyme involved in serotonin synthesis (Castro et al., 2013). In vitro, however, BPA has been shown to inhibit the release of serotonin, by decreasing exocytotic function of cells (Marquis and Haynes, 2010). Clearly, early BPA exposure can alter these systems, although it is unclear what implications these data have for the development or etiology of hyperactivity/ADHD in rodents and humans.

7. Conclusions

We have found, using the OHAT systematic review framework, that early exposure to BPA is a presumed health hazard linked to hyperactive behaviors in humans. This conclusion is based on the integration of animal and human literature in a rigorous analysis of the body of evidence that included evaluation of study quality, meta-analysis, and the consideration of other factors such as publication bias and dose-response. This review also identified data gaps and the need for additional risk assessments, including assessments of timing of exposure and a thorough dose-response analysis.

Although currently not widely used in the environmental science and regulatory arenas, systematic reviews such as this one are imperative for understanding the relationship between environmental exposures and health effects in humans. Likewise, systematic reviews and meta-analyses are valuable tools that should be used in order to translate science to policy for regulatory purposes, partly because they allow for the assessment of endpoints that might not be evaluated in traditional health regulatory assessments (e.g., behavioral or non-cancer disease endpoints). Current efforts to devise appropriate methods of assessing harmful chemicals should adopt systematic review as a valid means of hazard identification, due to its transparent, standardized and comprehensive procedures. Further, dose-response and exposure analyses are warranted to characterize the risks of BPA exposure, so that they can be effectively managed. In the meantime, given our conclusion that BPA is presumed to be a hazard to human health, steps should be taken to reduce exposure in the most vulnerable populations.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2017.12.028.

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Contributions

JRR and ALB conceived the research question, carried out the protocol and meta-analysis, and wrote the manuscript. CFK participated in the conception of the research question and writing and editing of the manuscript.

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