**Title:**

# Review of the Scientific Basis for the Document: Healthy Environments: Strategies for Avoiding Flame Retardants in the Built Environment

**Prepared For**

Energy Efficient Foam Coalition of the
American Chemistry Council

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## Introduction

The purpose of this review is to examine the scientific basis of the Perkins+Will report ("P+W Report") "Healthy Environments: Strategies for Avoiding Flame Retardants in the Built Environment" (Dedeo and Drake 2014). The first part of our review consists of general overarching comments. The second part is a detailed discussion of the various statements made in the report and their validity. A comprehensive literature search and evaluation, as well as weight of evidence assessments with regards to potential adverse effects often associated with flame retardants, is beyond the scope of the review. Likewise, we did not conduct a detailed review of the various biomonitoring studies used to support Perkins+Will's assertions regarding the detection of a large number of flame retardants in the human body.

We carefully reviewed the 47 citations contained in the End Notes and Work Cited table on pages 21-23 of the P+W Report. We obtained abstracts and, in most cases, full text articles for each of the references. The citations and links to abstracts are provided in (ANNEX 1). Also, for many of the scientific issues we addressed, we looked up other references that further inform the evaluation of the P+W Report. These are listed in the Reference section of this document.

Our careful consideration of the science relating to the human health impact of the flame retardants in the built environment shows that the P+W Report is fraught with unsupported generalizations and recommendations that are not well informed. Generally speaking, Perkins+Will did not critically review the references cited in their report with respect to the uncertainties associated with many of the conclusions drawn from them, even when the uncertainties and limitations are clearly articulated in those references. Moreover, they overlooked many peer-reviewed publications and government reports that carefully examined hazard, exposure, and resulting risk from various flame retardants used in the built environment. This oversight is reflected in a strong bias towards papers with provocative, yet poorly supported conclusions or papers that are limited in relevance to a single flame retardant or application. Nonetheless, these conclusions are often inappropriately extended to all flame retardants.

The claims that flame retardants are causally associated with various health effects in humans are largely without basis. We will show through a review of a broad range of human epidemiology and animal toxicology studies, that the P+W Report's implications of causality for cancer, diabetes, early puberty, longer times to get pregnant, and neurodevelopmental effects are not supported by the evidence cited.

## Part 1 – Overarching Comments

The concerns with the P+W Report can be placed into the following three categories:

1. Dismissal of Benefits of Flame Retardants
2. No Consideration of Quantifying Exposure and Risk
3. No Recognition of Extensive Review of Flame Retardant Hazard, Exposure, and Risk by Regulatory Authorities

A common theme throughout the P+W Report is the use of the non-specific term "flame retardants" when speaking about potential adverse health effects. As will be evident from the discussion below, such conclusions are applied in an overly broad fashion to implicate all flame retardant chemicals. Those conclusions are more appropriately limited to only the specific chemical class or single chemical that was the subject of a study.

### 1. Dismissal of Benefits of Flame Retardants

The P+W Report completely discounts or ignores the benefits of flame retardants. Moreover, the authors seem to imply that the only reason flame retardants are used in most cases is to comply with government regulations or building codes. There is no recognition that the regulations and codes are in place because of the public safety benefits that result from the use of flame retardants. The title of this document "Healthy Environments: Strategies for Avoiding Flame Retardants in the Built Environment" sums up this bias as well. Further, Perkins+Will claims that to avoid exposure to flame retardants "[t]he best solution is to avoid consumer products, building products, and finishes that contain flame retardants, to the extent possible."[1]

The purpose of the P+W Report is primarily to assess the relative hazards of the various flame retardants. Nonetheless, because the audience for the P+W Report (e.g., architects and designers) needs to consider all of the properties of materials or furnishings, it is unfortunate that the demonstrated benefits of flame retardants are not given more attention.

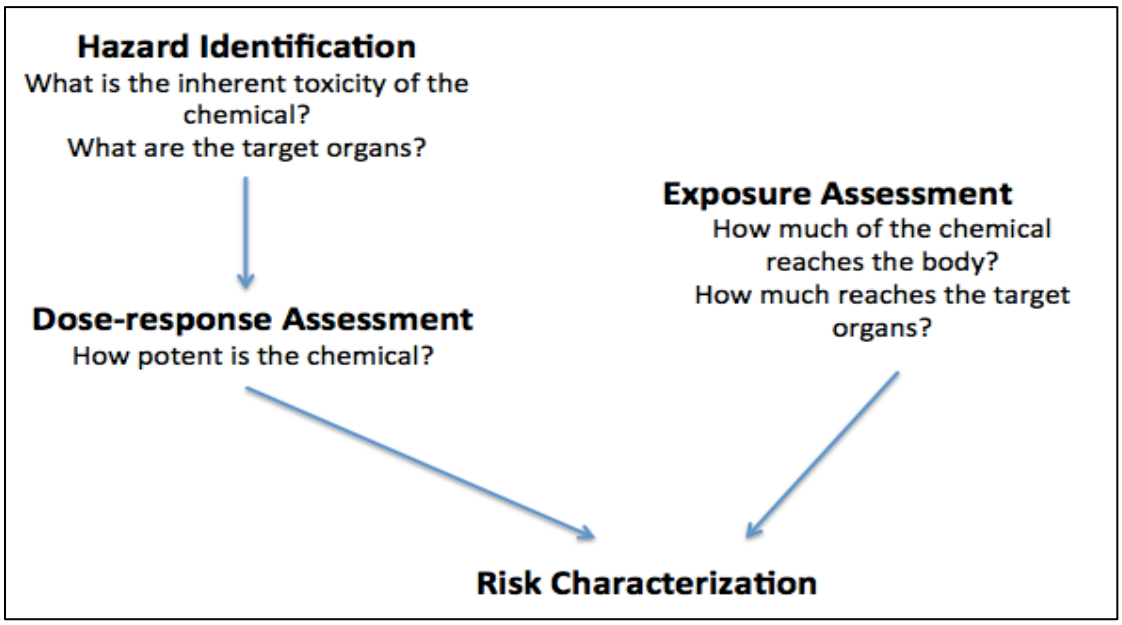
### 2. No Consideration of Quantifying Exposure and Risk

The P+W Report focuses primarily on the potential hazards of flame retardants and their presence in humans and the built environment. Scant consideration is given to risk, which is a function of both hazard (and its dose-response) and exposure. Figure

[1] Dedeo and Drake 2014, p. 6.
[2] NRC 1983, p. 19.
[3] Id.
[4] Id., p. 20.
[5] Id.
[6] Dedeo and Drake (2014), p. 10.
[7] Environment Canada and Health Canada 2013, p. 6.
[8] Id., p. 43.
[9] Environment Canada and Health Canada 2011, p. 50.

1 illustrates the classic risk assessment framework as first articulated by the National Research Council (NRC 1983).

**Figure 1: The NRC Risk Assessment Framework**




*Adapted from figure at USEPA 2015b.*

NRC (1983) defines the terms in each portion of the framework as follows.

> *Hazard Identification:* "[T]he process of determining whether exposure to an agent can cause an increase in the incidence of a health condition (cancer, birth defect, etc.)."[2] In addition, USEPA (2015b) says, "Factors such as the experimental route of exposure, the type and severity of the effects, the biological plausibility of findings, and the consistency of findings across studies all contribute to the hazard identification statement."
>
> *Dose-Response Assessment:* "[T]he process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent. It takes account of intensity of exposure, age pattern of exposure, and possibly other variables that might affect response, such as sex, lifestyle, and other modifying factors."[3]

[2] NRC 1983, p. 19.
[3] Id.

> *Exposure Assessment: "*[T]he process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment. In its most complete form, it describes the magnitude, duration, schedule, and route of exposure; the size, nature, and classes of the human populations exposed; and the uncertainties in all estimates."[4]
>
> *Risk Characterization:* "[T]he process of estimating the incidence of a health effect under the various conditions of human exposure described in exposure assessment. It is performed by combining the exposure and dose-response assessments."[5] The outcome is an estimate of the likelihood that a given hazard (specific toxic effect) will occur under a specified exposure scenario.

The P+W Report addresses exposure in a simple binary way: either there is human exposure or there is not. The authors make no attempt to quantify the exposure and rank the relevance of potential exposure sources. The P+W Report merely lists the presence of the flame retardants in various compartments:

> "The research shows that 31 flame retardants have been discovered in building and household products, 51 discovered in the indoor dust or air, and 33 have been discovered in people. The overlap between these lists is striking, as more than half of the flame retardants identified in products have also been found in the indoor environment and people's bodies. This strongly suggests that our body burden reflects our indoor environment, and that building products contribute to this exposure."[6]

With regards the declaration of certain flame retardant being detected in people's bodies, it is important to note that biomonitoring (measurement of the chemical in biological substances; e.g., blood and urine) data showing a chemical in the body tissue does not necessarily correlate with a certainty of potential to cause harm. The Centers for Disease Control and Prevention (CDC 2009) emphasizes this point:

> "The presence of an environmental chemical in people's blood or urine does not mean that it will cause effects or disease. The toxicity of a chemical is related to its dose or concentration, in addition to a person's individual susceptibility. Small amounts may be of no health consequence, whereas larger amounts may cause adverse health effects. Research studies, separate from the *National Exposure Report*, are required to determine the levels of a chemical that may cause health effects and the levels that are not a significant health concern."

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[4] Id., p. 20.
[5] Id.
[6] Dedeo and Drake (2014), p. 10.

Exposure must be considered when attempting to interpret biomonitoring data. For example, Aylward and Hays (2011) examined HBCD exposure levels in all available (published) human biomonitoring studies and concluded the following:

- Biomonitoring studies include exposures from all sources including possible exposure during use of products containing HBCD and all possible environmental sources, including dusts, dietary sources, etc.
- No effect levels were then determined in laboratory animal studies in government safety assessments such as those conducted by Environment Canada/Health Canada and the European Chemicals Bureau.
- These safety assessments included effects from all test endpoints in all of the laboratory animal studies to determine the "point of departure," the dose used for calculation of the hazard level in the risk assessment. Typically the point of departure is the lowest no effect level or a statistical estimate of this dose.
- Average human exposure levels in biomonitoring studies were 6000 to 100,000 times lower than the Point of Departure (i.e., the No Observable Adverse Effect Level in rat studies).
- These large margins of exposure indicate no reason for concern regarding human exposure to HBCD.

*Risk Management*

Risk Management is separate from the risk assessment process and is the stage when identified risks are mitigated. Among the ways this can occur is by chemical substitution or reduction in exposure potential. Perkins+Will lists hazards that are purported to be associated with flame retardants, primarily through a non-critical review of the literature and skips consideration of the dose-response for the effects (potency), the potential exposure to humans, and an integrated characterization of risk. The P+W Report lists potential hazards and rushes immediately to risk management.

## 3. No Recognition of Extensive Review of Flame Retardants by Regulatory Authorities

Contrary to Perkins+Will's assertion about the lack of health and safety data, many flame retardants have been extensively tested in the laboratory for mammalian and environment health effects. Subsequently, these data serve as the basis for analyses by regulatory agencies worldwide. Flame retardants for which extensive regulatory reviews have been conducted include, but are not limited to, the following:

- Hexabromocyclododecane (HBCD) – HBCD is the most commonly used flame retardant in polystyrene foam insulation.
- Tetrabromobisphenol A (TBBPA), TBBPA bis(allyl ether), TBBPA bis(2-hydroxyethyl ether) – These substances are incorporated into polymers as a

reactive or additive flame retardant for use in flame-retarded epoxy and polycarbonate resins and, to a lesser extent, in acrylonitrile-butadiene-styrene (ABS) resins and phenolic resins.
- Tris(1,3-dichloro-2-propyl) phosphate (TCPP) – TCPP is mostly used in rigid polyurethane foam insulation in the construction industry.
- Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP) – TDCP's primary uses are in flexible foams in the automobile and furniture industries.

The failure to refer readers to, or even acknowledge the existence of, the various evaluations of the hazard, exposure, and risk of flame retardants by regulatory authorities is a glaring weakness in the P+W Report. Countless hours have been expended by these agencies to carefully analyze the data and in some cases, to consider stakeholder comment during the assessment process. Some of the significant examples of regulatory reviews are summarized below.

**Environment Canada and Health Canada Assessment of TBBPA and Related Compounds**

The Canadian Environmental Protection Act (CEPA; Government of Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances of potential concern to determine whether they present or may present a risk to the environment or to human health. Following an extensive review of available hazard and exposure data for TBBPA, TBBPA bis(allyl ether), and TBBPA bis(2-hydroxyethyl ether) (Environment Canada and Health Canada 2013), they concluded that the three substances:

- "[A]re not entering the environment in quantities or concentrations or under conditions that constitute or may constitute a danger in Canada to human life or health . . ."[7] and

- "[A]re not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends."[8]

**Environment Canada and Health Canada Assessment of HBCD**

HBCD was also evaluated under CEPA (Environment Canada and Health Canada 2011). Regarding potential human health risks, the Canadian authorities concluded "HBCD is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health."[9]

[7] Environment Canada and Health Canada 2013, p. 6.
[8] Id., p. 43.
[9] Environment Canada and Health Canada 2011, p. 50.

**European Chemicals Bureau Assessment of TBBPA**

In 2006, the ECB published a risk of assessment of TBBPA (ECB 2006). The analysis examined multiple endpoints—acute toxicity, irritation, corrosivity, sensitization, repeated dose toxicity, mutagenicity, carcinogenicity, and reproductive toxicity—from inhalation, ingestion, dermal exposure routes. The Bureau's conclusions were as follows:

- Regarding human health, "No health effects of concern have been identified for TBBPA."[10]
- Regarding workers, "No health effects of concern to adults have been identified." Furthermore, "There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already."[11] This conclusion applied "in relation to all endpoints and for all exposure scenarios."[12]
- Regarding consumer exposure, "consumer exposure is negligible" and the findings were identical to those for workers for all endpoints.[13]

**European Chemicals Bureau (2008a) Assessment of TCPP**

The ECB's 2008 assessment of TCPP examined the same hazard inputs and exposure routes as the TBBP study described immediately above. For TCPP, ECB found:

- Regarding risk to the environment, "There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already."[14] The study also noted that TCPP meets neither the bioaccumulation nor toxicity criteria for PBT substance designation.
- ECB made the same conclusion with respect to potential risk workers, consumers, humans exposed via the environment, and combined exposure (i.e., adding consumer and environmental exposure).[15]

**European Chemicals Bureau Assessment of TDCP**

The ECB's 2008 assessment of TDCP (ECB 2008b) is similar to the TCPP assessment described above. For TDCP, ECB found:

- For environmental toxicity, "There is at present no need for further information and/or testing and no need for risk reduction measures beyond

[10] European Chemicals Bureau 2006, p. VI.
[11] Id.
[12] Id.
[13] Id.
[14] ECB 2008a, p. 8.
[15] Id. p. 14.

those which are being applied already."[16] The study also noted that TDCP meets neither the bioaccumulation nor toxicity criteria for PBT substance designation.

- With respect to human health and consumer exposure, "There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already." The conclusion "applies to all consumer exposure scenarios for the endpoints acute toxicity, irritation, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity, effects on male fertility, and developmental toxicity."[17]
- The ECB noted a lack of data on female fertility and reviewed other data to determine if risk could still be characterized for this endpoint. They brought forward a Lowest Observed Adverse Effect Level (LOAEL)[18] of 5 mg/kg that was derived for repeated dose toxicity and carcinogenicity. Given the low LOAEL derived from this study and a corresponding analysis by Janer et al. (2007), the ECB assessors determined that "the endpoint for female fertility is likely to be already covered by the LOAEL derived from the chronic study and any risk for female fertility will be addressed within the risk characterisation for repeated dose toxicity and carcinogenicity."[19]

**European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM Scientific Opinion on TBBPA**

The European Commission directed EFSA's CONTAM Panel to deliver a scientific opinion on potential risks from TBBPA and its derivatives in food. The panel produced a comprehensive aggregate assessment that also included consideration of exposure to breast-fed infants with average or high milk consumption, as well as exposure to TBBPA in dust in homes, classrooms, and cars (CONTAM 2011). They concluded that:

- For consumers of fish and consumers of cow's milk (i.e., infants and small children), the margin of exposure (MOE) in the worst case exposure scenarios was several orders of magnitude below the default margin of exposure (100), "indicating that current dietary exposure to TBBPA for these population groups in the EU does not raise a health concern."[20]
- More generally, given the extremely low levels of TBBPA in food (below the level of quantification), "it is unlikely that current dietary exposure of the

[16] ECB 2008b, p. IX.
[17] Id.
[18] The International Union of Pure and Applied Chemistry's (IUPAC 2014)definition of LOAEL is: "Lowest concentration or amount of a substance, found by experiment or observation, which causes an adverse alteration of morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure."
[19] Id., p. 187.
[20] CONTAM 2011, p. 54.

general population to TBBPA raises a health concern."[21]

- Regarding breast-fed infants, "Exposure of breast-fed infants to TBBPA via human milk also shows very high MOEs . . . and therefore does not raise a health concern."[22]
- And finally, "combined exposure to TBBPA from food and dust, particularly for children, is unlikely to raise a health concern."[23]

**European Chemicals Bureau Assessment of HBCD**

The ECB's risk assessment of HBCD (ECB 2008c) found some need to explore occupational exposures, but also concluded the following:

- For consumers, "There is at present no need for further information and/or testing and for risk reduction measures beyond those, which are being applied already."[24]
- For human exposure via the environment, "There is at present no need for further information and/or testing and for risk reduction measures beyond those, which are being applied already."[25]

**U.S. Environmental Protection Agency Design for the Environment (DfE) Program**

The DfE Program has issued the following alternative assessments for flame retardants:

- An Alternatives Assessment for the Flame Retardant Decabromodiphenyl ether (DecaBDE) (USEPA 2014a)
- Flame Retardants Alternatives for HBCD: Final Report (USEPA 2014b)
- Flame Retardants Used in Flexible Polyurethane Foam: An Alternative Assessment Update (USEPA 2015a).

A DfE alternatives assessment identifies and compares potential chemical alternatives that can be used as substitutes to replace chemicals that the Agency has designated for special attention. The assessment criteria are primarily hazard-based human health and ecological toxicity endpoints, as well as environmental fate. The USEPA acknowledges that, although not part of the assessment, performance, cost, and efficacy of the alternatives are essential for an alternative to be viable.[26]

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[21] Id., p. 4.
[22] Id., p. 55.
[23] Id.
[24] ECB 2008c, p. 27.
[25] Id.
[26] "The DfE approach allows companies to examine hazard profiles of potential replacement chemicals so they can consider the human health and environmental attributes of a chemical in association with cost and performance considerations. . . While DfE does not assess performance considerations, these attributes are critical to the overall function and marketability of flame retardants." USEPA 2014b, p. 5-6.

Although the USEPA does not explicitly designate any of the alternatives as "acceptable," its analysis illustrates the varying spectrum of toxicological properties both between and within chemical classes. For example, in the alternatives assessment for HBCD, EPA identified potential alternatives that were less bioaccumulative and/or less toxic to aquatic organisms (that are therefore not PBTs).

A detailed discussion and critique of the DfE assessments is beyond the scope of this document. Nonetheless, they are a tremendous resource for fact-based analyses of currently used flame retardants and possible alternatives. Use of these data is far preferable to the broad-brush condemnation of entire chemical classes and use categories as recommended by Perkins+Will.

**Government of Australia National Industrial Chemicals Notification and Assessment Scheme (NICNAS) assessment of HBCD.**

NICNAS conducted an assessment of HBCD as part of its Priority Existing Chemical program. Regarding risks to human exposures through the environment, the assessors concluded the following:

- "Consumers using treated products (e.g. automotive upholstery) may be exposed to HBCD that diffuses out of the articles. Estimates of dermal exposure (main route) from this source indicate very low exposure and therefore low risk to adults as well as children." [27]
- "Indirect exposure to HBCD through the environment may occur by consumption of food and drinking water contaminated by HBCD and by inhalation of indoor and outdoor air. Exposure to HBCD from these sources appears to be low and hence low risk is expected."[28]
- "Toddlers may have the highest exposure to HBCD through ingestion and inhalation of dust/soil containing HBCD released from HBCD containing articles in the house, however, the risk of developing adverse health effects is low. The risk to infants through exposure to HBCD in breast milk is also estimated to be low."[29]

[27] NICNAS 2015
[28] Id.
[29] Id.

## Part 2 – Detailed Review of Scientific Basis for Statements

### Health Effects and Costs of Flame Retardants

The P+W Report cites that diabetes, neurobehavioral and developmental disorders, cancer, reproductive health effects, and alterations in thyroid function have been associated with exposure to flame retardants (page 7). The key word is "associated," which is a far less significant association than the causal relationship the authors imply. Although the authors properly point out that it is impossible to estimate what fraction of the disease cases they describe are due to specific chemical exposures, their implication that flame retardants are significant contributors is clear.

The reference for this statement is Kim et al. (Kim et al. 2014) who conducted a systematic review of studies on the health impacts of exposure to brominated flame retardants (BFRs) in humans, with a particular focus on children. They used articles discoverable through the MEDLINE and EMBASE electronic databases as of January 2012 to identify published cohort, cross-sectional, and case-control studies exploring the relationship between BFR exposure and various health outcomes. After applying certain inclusion criteria, 36 epidemiological studies were included in the review. Regarding their findings and conclusions, Kim et al. state that:

> "Plausible outcomes associated with BFR exposure include diabetes, neurobehavioral and developmental disorders, cancer, reproductive health effects and alteration in thyroid function. Evidence for a causal relationship between exposure to BFRs and health outcomes was evaluated within the Bradford Hill framework. CONCLUSION: Although there is suggestive evidence that exposure to BFRs is harmful to health, further epidemiological investigations particularly among children, and long-term monitoring and surveillance of chemical impacts on humans are required to confirm these relationships."[30]

A close look at this very detailed review shows that many of the studies reviewed address exposures to polybrominated biphenyls (PBBs). The manufacture of PBBs was banned in the United States in 1976 after an agricultural contamination episode in 1973 when PBB was accidentally mixed into animal feed, exposing millions of Michigan residents to contaminated dairy products, eggs and meat (MDCH 2011). The data on the PBBs have little relevance to the question of material or product selection facing architects today, and the chemicals reviewed in the Kim et al. review have little relevance to today's build environment. Unfortunately, the P+W Report does not appear to assess whether the studies it cites are relevant to its conclusions and recommendations.

The remainder of the studies cited in the report dealt with polybrominated diphenyl ethers (PBDE) exposure. Given that the PBDEs having largely been banned or

[30] Kim et al. (2014), p. 1.

phased out for new uses in United States elsewhere, these analyses are not relevant to the safety assessment of flame retardants currently being considered to be used in the built environment

**Neurodevelopmental Effects**

The generalizations with regards to neurodevelopmental effects are not supported by the data. The findings depend upon the flame retardant in question and the study conducted (summarized below).

The P+W Report discusses the link between the reported IQ loss due to PBDE exposure and claims it has been well studied. The authors suggest that the cost of the IQ loss due to exposure to this flame retardant exceeds $10 billion annually. The basis for this calculation is not clear. Two studies, discussed below, are cited when making this claim, but neither reference mentions a specific cost (Eskenazi et al. 2013; Miller-Rhodes et al. 2014).

*Animal Data*

The P+W Report claims that "flame retardants are linked to hyperactivity, and decreased attention, motor functioning, and IQ."[31]. The reference for this statement, (Woods et al. 2012), appears to be incorrect. Woods et al. report the use of a genetically and epigenetically susceptible mouse (Mecp2 truncation mutant mouse) with social behavioral defects to explore the long-lasting effects of PBDE exposure. Nowhere is hyperactivity, decreased attention, or IQ discussed.

Most recently Cope et al. (2015) reported on a series of studies on TBBPA dosed orally to rats over the course of 2 generations on growth as well as behavioral, neurological and neuropathological functions in offspring. In a separate study the influence of oral exposure to TBBPA was examined on rat embryonic/fetal development from gestation days (GDs) 0–19. In the reproductive study, exposure to either 100 or 1000 mg/kg/day TBBPA resulted in a decrease in circulating, peripheral thyroxine (T4) levels in rats that were not accompanied by any marked alterations in triiodothyronine (T3) and thyroid stimulating hormone (TSH). These findings are explainable on the basis of induction of rat liver catabolism, a phenomenon that may be species-specific and not relevant for humans. TBBPA at up to 1000 mg/kg BW/d was not associated with any significant non-neurological effects on reproduction, growth and development. No TBBPA-related effects on developmental neurotoxicity/neuropathology were detected. In the developmental study no TBBPA-related change in mortality rate or other effects were observed in any of the mothers at any dose. The No Observed Effect Level (NOEL)[32] for maternal and developmental toxicity was 1000 mg/kg/day, the highest dose evaluated.

[31] Dedeo and Drake 2014, p. 7.
[32] From IUPAC 2014: "Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity,

Miller-Rhodes et al. (2014) examined some of the developmental and lifelong neurobehavioral effects of prenatal hexabromocyclododecane (HBCD) exposure in which pregnant rats were gavaged with 0, 3, 10, or 30 mg/kg HBCD from GD 1 to parturition. A functional observation battery was used to assess sensorimotor behaviors in neonates, and locomotor and response evaluations were made in cohorts of young adult and aged rats. HBCD exposure was associated with increased reactivity to a tailpinch in neonates, decreased forelimb grip strength in juveniles, and impaired sustained attention indicated by go/no-go responding in aged rats. The relevance of these data to humans is not known.

Biesemeier et al. (2011) report the results of a developmental neurotoxicity study in which DecaBDE was administered orally in corn oil to pregnant females from GD 6 to weaning (postnatal day 21). Standard measures of growth, development, and neurological endpoints were evaluated in the offspring. Motor activity was assessed at 2 months of age. Additional motor activity assessments were conducted at 4 and 6 months of age. Neuropathology and morphometry evaluations of the offspring were performed at weaning and adulthood. No treatment-related neurobehavioral changes were observed in detailed clinical observations, startle response, or learning and memory tests. No test substance-related changes were noted in motor activity assessments performed at 2, 4, or 6 months of age. Moreover, no treatment-related neuropathological or morphometric alterations were found. The No Observed Adverse Effect Level (NOAEL)[33] was the highest dose tested (1000 mg/kg).

Prior to the publication of the above papers, Williams and DeSesso (2010) reviewed all 29 available studies with PBDE congeners, HBCD, or TBBPA in which animals were dosed perinatally, either during gestation or within 3 weeks of birth (i.e., prior to postnatal day 21) and for which specific neurobehavioral assessments were performed They stated that:

> "In conclusion, although the results of some of the experimental animal studies of perinatal exposure to PBDE congeners and HBCD are provocative, as a whole, they do not provide evidence of consistent alterations in motor activity and should not be used as the basis for establishing toxicity reference values."[34]

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growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure."

[33] From IUPAC 2014: "Greatest concentration or amount found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions."

[34] Williams and DeSesso (2010), p. 442.

In addition:

> "The lack of consistency across studies precludes establishment of a causal relationship between perinatal exposure to these substances and alterations in motor activity."[35] (page 411)

It is unclear that animal data, including the one study cited in the P+W Report support the assertion that neurodevelopmental effects are caused by exposure to flame retardants.

*Human Data*

In addition to the animal studies discussed above, some epidemiology studies have addressed this topic in humans as well. Because many factors can influence neurodevelopment of humans, extraordinary efforts must be made to control for these confounders in epidemiology studies. In many cases, they cannot be controlled, so such studies are best considered to be examining possible associations rather than assessing causality. Thus, they are usually hypothesis generating rather than hypothesis testing. Two of the more noteworthy studies are presented below.

Eskenazi et al. (2014) reported an investigation into the relationship of *in utero* and child PBDE exposure to neurobehavioral development among participants in CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas), a California birth cohort. They measured PBDEs in maternal prenatal and child serum samples and examined the association of PBDE concentrations with children's attention, motor functioning, and cognition at 5 (n = 310) and 7 years of age (n = 323). Maternal prenatal PBDE concentrations were associated with impaired attention as measured by a continuous performance task at 5 years and maternal report at 5 and 7 years of age. PBDE concentrations in children 7 years old were significantly or "marginally" associated with concurrent teacher reports of attention problems and decrements in other cognitive measures. These associations were not altered by adjustment for birth weight, gestational age, or maternal thyroid hormone levels. The authors' perspective on the study follows:

> "Important strengths of the current study include its longitudinal design and use of comprehensive neurobehavioral assessments, which incorporate input from multiple informants. Limitations of this study are that we did not observe consistency in associations with PBDEs across informants for measures of attention (although their responses were moderately correlated), and we constructed numerous statistical models (although

[35] Id. p. 411.

> performance across domains was also moderately correlated), which increased the possibility of a chance finding."[36]

Limitations notwithstanding, this paper has been cited in numerous regulatory and legislative forums as convincing evidence for the claim that flame retardants cause a decrease in children's' IQ. The P+W Report suffers from the same lack of attention to the study authors' interpretation of their own work.

Insight to this topic also comes from Roze et al. (2009), who reported the results of a segment of the prospective Groningen (Netherlands) infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) study. It included 62 children in whose mothers a suite of chemicals, including BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, and HBCD, was measured in the 35th week of pregnancy. Thyroid hormones were measured in umbilical cord blood. When the children were 5–6 years of age, their neuropsychological functioning was assessed by the following: motor performance (coordination, fine motor skills), cognition (intelligence, visual perception, visuomotor integration, inhibitory control, verbal memory, and attention), and behavior. The results were intriguing:

> "Brominated flame retardants correlated with worse fine manipulative abilities, worse attention, *better* coordination, *better* visual perception, and *better* behavior."[37] (emphases added)

This illustrates a not uncommon outcome from epidemiology studies in which many effects are analyzed and various models are used to best fit the data. This often results in apparent relationships that may have arisen by chance alone. The authors commented that:

> "It was striking that we found both positive and negative correlations between OHC [organohalogen compounds] and outcome. It is difficult to determine the implications of these results for functioning in later life. The multiple statistical analyses that were performed might have played a role in this finding. Furthermore, it is difficult to determine how many of these effects can reliably be assigned to the specific contaminants, because some of them were likely to show some degree of collinearity. Other contaminants that were not measured, such as methyl mercury, might also have played a role."[38]

**Endocrine Disruption**

The P+W Report states that flame retardants are linked to obesity, diabetes, early

[36] Eskenazi et al (2014), p. 261.
[37] Roze et al. 2009, p. 1953.
[38] Id., p. 1957.

puberty, and longer times to become pregnant and strongly implies that some portion of the $245 billion cost associated with diagnosed diabetes cases can be attributed to flame retardants.[39] We critically review the science supporting such strong assertions in the sections that follow.

With regards to endocrine effects in general, Colnot et al. (2014) reviewed the results of a variety of previously unpublished and published animal studies evaluating the effects of TBBPA after repeated exposure on reproductive and developmental parameters. They concluded that no biologically significant adverse effects on endpoints potentially related to interferences with the endocrine system by TBBPA were evident.

*Early Puberty*

The reference cited in the P+W Report, Chen et al. (Chen et al. 2014), does not actually address this topic. However, we searched the literature for relevant animal and human studies and found three papers that address this endpoint. The results are far from conclusive, as explained below

In one study (Patisaul et al. 2013), a commercial mixture of triphenyl phosphate (TPP); a mixture of isopropylated triphenylphosphate isomers (ITPs); 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB); and bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBPH) caused a statistically significant early onset of puberty in the high dose (1 mg/kg) female rats.

In another study (Lilienthal et al. 2006), 2,2´,4,4´,5-pentabromodiphenyl ether (PBDE-99) caused an advanced onset of puberty in the high-dose females rats, an effect that was associated with elevated body weight. In contrast, the lower dose resulted in a slight acceleration of puberty onset in male rats compared with controls. Exposure decreased circulating estradiol and testosterone in male offspring at weaning and in adulthood. No effects were noted in female offspring at weaning. In contrast to the males, circulating sex steroids were not measured in females at adulthood. Anogenital distance was reduced in male offspring. The Lowest Observable Adverse Effect Level (LOAEL) was 1 mg/kg.

Finally, as part of the evaluation of the Pubertal Assay to be used in the USEPA's Endocrine Disruptor Screening Program, DE-71 (a commercial mixture which contains mostly tetra and penta PBDE congeners) was shown to cause significantly delays in preputial separation[40] (PPS) in males at doses of 30 and 60 mg/kg/day and a significant delay in the age of vaginal opening[41] in females at the 60

[39] Dedeo and Drake 2014, p. 7.
[40] Preputial separation is the separation of the prepuce from the glans penis. It is androgen-dependent and used as an indicator the onset of puberty in male rats (Korenbrot et al 1977).
[41] An indicator of pubertal onset in female rats.

mg/kg/day dose. No effects were noted at 3 mg/kg/day (Stoker et al. 2004).

Table 1 below shows that the doses causing effects in rats are much higher than anticipated human exposure levels and the EPA Reference Doses for some PDBE congeners (USEPA 2014c).

Table 1: EPA Reference Doses for Selected PBDE Congeners

| Chemical | Reference Dose (mg/kg/day) | Relevant Dose in Animal Study (mg/kg/day)_ | Estimated Daily Exposure (total PDBE) (mg/kg/day)_ | Fraction of RfD Represented by Exposure |
|---|---|---|---|---|
| TetraBDE | $1 \times 10^{-4}$ | LOAEL=1 Lilienthal et al., 2006 | Adult = $7.1 \times 10^{-6}$<br>Child (1-5) = $4.7 \times 10^{-5}$<br>Child (6-11) = $1.3 \times 10^{-5}$ | Adult = 0.07<br>Child (1-5) = 0.47<br>Child (6-11) =0.13 |
| PentaBDE | $2 \times 10^{-3}$ | NOAEL = 3 Stoker et al., 20045 | Adult = $7.1 \times 10^{-6}$<br>Child (1-5) = $4.7 \times 10^{-5}$<br>Child (6-11) = $1.3 \times 10^{-5}$ | Adult = 0.0036<br>Child (1-5) = 0.024<br>Child (6-11)= 0.0065 |

*Obesity*

HBCD is both persistent and lipophilic and has been detected in human adipose tissue, particularly in obese individuals (Malarvannan et al. 2013). Yanagisawa et al. (2014) investigated the possibility that HBCD may play a role in causing the obesity. The authors studied HBCD's effects in mice fed either a high fat diet (HFD) or normal diet (ND) and reported that:

> "The present study showed that enhanced weight gain, hyperglycemia, hyperinsulinemia, hepatic steatosis, and macrophage accumulation in adipose tissue in HBCD-treated HFD-fed mice but not in HBCD-treated ND-fed mice. These results suggest that HBCD may contribute to metabolic dysfunction via an interaction with diet (i.e., HBCD may be an "enhancer" obesogen). We found that HBCD contributes to the progression of diet-induced weight gain and metabolic dysfunction, suggesting that HBCD may increase the risk of diet-induced obesity."[42]

The possible ability of chemicals to cause metabolic disturbances leading to obesity is a controversial one, and sorting out the role of chemicals is complicated by genetic diversity and widely varying dietary habits in the human population, among other confounding factors. Although provocative, it is important to note that the effects reported only occurred in mice fed a high fat diet. Moreover, there is no

[42] Yanagisawa et al 2014, p. 282.

widely accepted animal model for the prediction of obesity induction in humans by chemicals; the relevance of these results therefore remains uncertain.

*Diabetes*

Type 2 (adult onset) diabetes is a complex disease that has a significant impact in the more developed nations. Identifying risk factors with the intent of reducing their role in causing the disease is a major research effort in the US and elsewhere.

The basis for the claim with regards to diabetes in the P+W Report appears to have come from the Kim et al. (2014) review of brominated flame retardants, which cites three studies, two of which relate to the long banned PBBs and one of which looks at PBDE and diabetes in people with hypothyroid disease. They found no elevated risk of diabetes in the PBDE-exposed population.

According to the National Institutes of Health (NIH), people who have one of more of the following characteristics are more likely to develop Type 2 diabetes (NIH 2014):

- Age 45 or older
- Overweight or obese
- Physically inactive
- Parent or sibling with diabetes
- Family background that is African American, Alaska Native, American Indian, Asian American, Hispanic/Latino, or Pacific Islander American
- History of giving birth to a baby weighing more than 9 pounds
- History of cardiovascular disease
- History of gestational diabetes
- High blood pressure - 140/90 or above - or being treated for high blood pressure
- High-density lipoprotein (HDL) below 35 mg/dL, or a triglyceride level above 250 mg/dL
- Polycystic ovary syndrome, also called PCOS
- *Predieteacosis nigricans*, a condition associated with insulin resistance, characterized by a dark, velvety rash around the neck or armpits

In addition, some medications, such as nicotinic acid and certain types of diuretics, anti-seizure drugs, psychiatric drugs, and drugs to treat human immunodeficiency virus (HIV), may lead to diabetes by impairing pancreatic beta cells or disrupting insulin action. Pentamidine, a drug prescribed to treat a type of pneumonia, can increase the risk of pancreatitis, beta cell damage, and diabetes. Glucocorticoids, used to treat inflammatory illnesses such as rheumatoid arthritis, asthma, lupus, and ulcerative colitis may impair insulin action (NIH 2014).

With specific regards to environmental chemicals associated with diabetes in humans, many chemicals are toxic to beta cells in animals, but only a few have been

linked to diabetes in humans (NIH 2014). No mention of flame retardants in the context of diabetes is made by the NIH.

*Longer Time to Get Pregnant*

The P+W Report's claim that exposure to flame retardants in the built environment may lead to longer times to get pregnant appears to be based on a report by Harley et al. (2010). As part of the CHAMACOS study (Eskenazi et al. 2013) mentioned above, 343 women had PBDEs measured in serum collected during pregnancy. The beginning of the pregnancy was determined by asking the woman the date of her last menstrual period (LMP) or, if she did not know (4%), by using the LMP estimate from the clinical ultrasound. Women were then asked the number of months it had taken to get pregnant (i.e., for how many months had you been having sexual intercourse without doing anything to prevent pregnancy?).

The interval between stopping contraception and becoming pregnant was considered the "time-to-pregnancy period" and was marked on the calendar to aid recall about exposures during that time period. Women were also asked whether they had had regular menstrual periods in the year before the pregnancy and, if so, how many days were in her cycle. Additional questions asked about hormonal contraceptive use in the year before the pregnancy, frequency of intercourse, use of fertility medication, use of contraception (either regularly or inconsistently) during the month of conception, and whether she had been actively trying to get pregnant. Information about various possible confounders was collected as well. The results were that:

> "After controlling for confounders, each 10-fold increase in the concentration of BDE-100 and BDE-153 was associated with a 40% decrease [fOR = 0.6; 95% confidence interval (CI), 0.4–0.9; $p < 0.01$] and 50% decrease (fOR = 0.5; 95% CI, 0.3–0.8; $p < 0.01$), respectively, in the odds of achieving pregnancy in each month. BDEs 47 and 99 were also associated with 20–30% lower odds of pregnancy, but these findings were of borderline statistical significance ($p = 0.07$ and $p = 0.11$, respectively). When concentrations of all four congeners were summed, a 10-fold increase in the sum PBDEs was associated with 30% decreased odds of pregnancy each month."

Harley et al. commented that:

> "This study is the first to report that higher PBDE concentrations in women's blood are associated with significantly longer time to pregnancy, and this finding needs to be replicated in other populations. The study population of predominantly Mexican immigrants living in an agricultural community is a distinctive group, and findings may not be generalizable to all women. The relationship among PBDE exposure, length of time in the United States, and fertility is somewhat complex. Although we controlled for both time in the United States and pesticide exposure, this study should be replicated in a

> population that is not subject to these factors. If confirmed, this finding would have strong implications to women trying to conceive given that exposure to PBDEs is nearly universal in the United States and many other countries."

The study suggests an association between PBDE levels and time to pregnancy, but drawing a causal link is not possible. This is a lone study of an atypical population. As with many such epidemiology studies, a more exhaustive consideration of confounding factors is needed, and well as confirmatory studies that take these confounders into account.

**Cancer**

Cancer is the second-leading cause of death among Americans. One of every four deaths in the United States is due to cancer (CDC 2015). In 2012, 1,529,078 Americans received a new diagnosis of invasive cancer, and 582,607 Americans died of the disease (CDC 2015). The causes of cancer in humans are many fold but generally relate in one way or another to mutation of the genetic material in cells. As the Mayo Clinic (2015) notes:

> "A number of forces can cause gene mutations, such as smoking, radiation, viruses, cancer-causing chemicals (carcinogens), obesity, hormones, chronic inflammation and a lack of exercise."

With respect to humans, we are aware of one investigation (Zhang and Rusiecki 2012), into the possible association of PBDEs and thyroid cancer. The first part of the study is a population-based case-control study, examining links between PBDEs and the risk of thyroid cancer using all cases of thyroid cancer diagnosed in Connecticut in 2010 and 2011 and age- and gender-matched general populations in Connecticut. The second and more extensive project is a longitudinal study in collaboration with the CDC and the Department of Defense (DOD). Using serum from the DOD Serum Depository, Zhang and her colleagues are attempting to examine the role of PBDEs in the development of thyroid cancer in 800 cases and 800 controls between 2000 and 2012.

Because of the complexity and other limitations associated with epidemiology studies such as the one reported above, prediction of carcinogenicity in humans usually relies upon the assessment of such potential in rodents. Lifetime cancer bioassays are conducted in rats and mice at doses ranging from the Maximum Tolerated Dose (MTD)[43] at the high end, down to doses that have little or no toxicity

[43] From IUPAC 2014: "High dose used in chronic toxicity testing that is expected on the basis of an adequate subchronic study to produce limited toxicity when administered for the duration of the test period. It should not induce: (a) overt toxicity, for example appreciable death of cells or organ dysfunction, or (b) toxic manifestations that are predicted materially to reduce the life span of the animals except as the result of neoplastic development or (c)

to the animals. The use of MTD testing has often been criticized, especially in the case of chemicals shown not to damage the DNA (i.e., non-genotoxic) (Cohen 1998). Many such non-genotoxic rodent carcinogens are regarded to exhibit thresholds for carcinogenicity, especially when some knowledge about the underlying mode of action for the tumor formation is available (European Commission, 2009).

Various regulatory agencies such as USEPA, European Chemicals Agency (ECHA), International Agency for Research on Cancer (IARC), and the California Office Environmental Health Hazard Assessment (OEHHA) evaluate the results of lifetime cancer bioassays and generally place the chemical into one their respective classification schemes. For example, California OEHHA uses the results to determine whether a chemical should be placed on the Proposition 65 list of chemicals "Known by the State of California to be Carcinogenic." The application of the results of this testing is a complex and, often controversial exercise. Some flame retardants have been classified as "carcinogenic to laboratory animals" based on the results of such lifetime bioassays. These include: TBBPA, TCEP, and TDCPP. Lifetime cancer studies on TCPP are in progress and results are expected in 2016.

Although a chemical may be shown to be carcinogenic in animal studies, extrapolation of those results to humans is a difficult exercise, one that is best undertaken with some knowledge of the Mode of Action[44] by which the chemical causes tumors in animals (Sonich-Mullin et al. 2001). That knowledge is essential to the assessment of the relevance of the animal findings to humans. Few flame retardants have been critically evaluated with respect to the human relevance of the bioassay findings. In the absence of such an evaluation, regulatory actions usually proceed on the basis that the results are at least qualitatively relevant to humans.

Note: Recently, a Mode of Action analysis has been published for TBBPA (Lai, Kacew, and Dekant 2015). The authors provide evidence suggesting that TBBPA causes uterine tumors in rats by a threshold-based mode of action. Considering the pharmacokinetic aspects of the lifetime rodent cancer bioassay in which tumors were produced (daily oral gavage of high doses of TBBPA) relative to the potential exposure of humans to TBBPA-containing dust, the authors concluded, "Due to the absence of a genotoxic MoA for uterine tumor induction by TBBPA and the low levels of human exposure, a tumor risk in humans after environmental exposures to TBBPA is expected to be low."

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10% or greater retardation of body weight gain as compared with control animals. In some studies, toxicity that could interfere with a carcinogenic effect is specifically excluded from consideration."

[44] From USEPA 2009: "A sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in an adverse health effect."

## Summary

The P+W Report presents a narrow view of the topic of flame retardants in the built environment. Generally speaking, the following deficiencies characterize the report:

1. Dismissal of Benefits of Flame Retardants
2. No Consideration of Quantifying Exposure and Risk
3. No Recognition of Extensive Review of Flame Retardant Hazard, Exposure, and Risk by Regulatory Authorities

Furthermore, the references cited in the P+W Report were not reviewed critically with respect to the uncertainties associated with many of the conclusions drawn from them, even when the uncertainties and limitations are clearly articulated in those same references. Moreover, Perkins+Will overlooked many peer-reviewed publications and government reports that carefully examined hazard, exposure, and resulting risk from various flame retardants used in the built environment. This oversight is reflected in a strong bias towards papers with provocative, yet poorly supported conclusions or papers that are limited in relevance to a single flame retardant or applications. Nonetheless, these conclusions are often inappropriately extended to the entire category of flame retardants.

The claims that flame retardants are associated with (and the implication that they cause) various health effects in humans are largely without basis. Through a review of a broad range of human epidemiology and animal toxicology studies, we have shown this for claims of cancer, diabetes, early puberty, longer times to get pregnant, and neurodevelopmental effects.

In conclusion, a careful consideration of the science relating to the human health impact of the flame retardants in the built environment shows that the P+W Report is fraught with unsupported generalizations and recommendations that are not well informed.

We recommend that Perkins+Will should more fully examine the strengths and weaknesses of *all* of the available data on the topic and develop more fact-based guidance for the selection of flame retardants in the built environment. This would also include a detailed review of the various biomonitoring studies used to support the assertions made regarding the detection of a large number of flame retardants in the human body.

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