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Partners in Science

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The Endocrine Disruption Exchange (TEDX) is submitting comments regarding the Children's Safe Product Act (CSPA) rule (WAC 173-334). We are an internationally recognized non-profit organization that partners with government, academic, and industry scientists to evaluate, translate and disseminate scientific evidence of endocrine disruption. We declare that we have no direct or indirect financial or fiduciary interest in the manufacture or sale of any chemical that would be the subject of the deliberations of this rule amendment.

We appreciate the opportunity to provide comments on this rule amendment. The proposed updates to the rule WAC 173-334 aim to add an additional 21 chemicals to the list of chemicals that must be reported to the State of Washington Department of Ecology as chemicals of high concern to children (CHCC list). In addition, the proposed rule aims to delist or otherwise remove 3 chemicals from the CHCC list. The proposed rule will be the first major update to the CHCC list since its inception in 2011, with the exception of a single listing and delisting in 2013, and represents significant progress towards improving exposure characterization of chemicals of high concern to children. We respectfully submit these comments in response to the Department of Ecology's proposed rule.

In summary, our comments address the following main points:

1. **We support the addition of 21 new chemicals to the CHCC list;**
2. **We support consideration of chemicals submitted for this rule update but not included in the current proposal;**
3. **We do not support the removal of D4 from the CHCC list.**

Thank you for the opportunity to provide these comments. Please let us know if we can provide any additional information or be of further help.

Respectfully,

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Background

We appreciate the opportunity to provide comments on the Department of Ecology's proposed rule to amend WAC 173-334 which would add 21 chemicals and remove 3 chemicals from the CHCC list of chemicals that must be reported to the Department of Ecology when they occur in children's products. The creation of the CHCC list in 2011 has been an invaluable tool for environmental health scientists who aim to determine if a given chemical poses harm to children. In general, it is often far too difficult for consumers and environmental health scientists to estimate potential exposures to chemicals because of the lack of transparency about chemicals used in every-day consumer products. The implementation of WAC 173-334 and the CHCC list helps to fill a data need that allows environmental health scientists to begin to understand pathways of exposure. **It is crucial that the State of Washington continue to lead the way in chemical disclosures.**

Endocrine disrupting chemicals (EDCs) are chemicals made outside of the body that can block, mimic or otherwise disrupt normal hormone signals. Disturbances to normal hormonal signaling can lead to diseases and poor health conditions. This is because the endocrine system is a complex chemical messaging system that is involved in every stage of life, from conception through gestation, birth, puberty, adulthood and senescence. Hormones operate at very low levels to control many of life's functions. Therefore, exposures to EDCs, even at very low levels during certain times of life can have varying and dramatic impacts. **Fetal development and childhood are critical periods for exposure** because the endocrine system orchestrates many developmental processes and thereby sets the program for how the body will respond to the environment throughout life. In other words, disturbances to normal hormonal signaling early in life can have long lasting consequences.

We breathe, eat, drink, and touch EDCs every day. EDCs can be components of plastics, pesticides, flame retardants, fragrances and more. EDCs are in many common items such as toys, clothing, cosmetics, sunscreens, electronics, furniture, cleaning products, lawn care products, automobiles, building materials, food, and food packaging. However, due to their ubiquity in our modern life and the lack of federal laws requiring reporting of most chemicals used in consumer products, it is difficult for environmental health scientists to fully and accurately characterize potential sources of exposure and exposure pathways. **Reporting of chemical levels in children's products on the CHCC list addresses this data gap and provides an invaluable resource to environmental health scientists engaged in hazard identification, policy makers, and consumers who are eager to make informed purchasing decisions.**

Specific Comments

1. Support for the addition of 21 new chemicals to the CHCC list.

As indicated above, there is a systematic lack of transparency regarding the potential for exposure to EDCs and other environmental chemicals in consumer products. Given that children are particularly susceptible to the potentially damaging effects of exposure to EDCs and other environmental chemicals, it is imperative that steps are taken to begin to identify potential exposure sources. We support any efforts that aim to improve the transparency and reporting of chemical usage in consumer products, especially those that are marketed specifically to children as they are considered a vulnerable population.

Of the proposed 21 new chemicals to the CHCC list 16 have evidence of endocrine disrupting activity. As such, determining the potential for exposure from children's products should be considered high priority.

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We thank Ecology for noting the endocrine activity of these 16 chemicals and have provided additional information highlighting their potential endocrine disrupting activity:

- **Bisphenol F** (BPF: 620-92-8): BPF induces the uterotrophic response in weanling rats [1] and disrupts thyroid hormone signaling in sub-chronically exposed rats [2]. In *in vitro* studies BPF shows similar potency to BPA across more than 38 different studies reporting estrogen receptor activation or antagonism, androgen receptor activation and antagonism, and glucocorticoid receptor antagonism [3].

- **Bisphenol S** (BPS: 80-09-1): BPS induces the uterotrophic response in weanling rats [1] and is a reproductive toxicant in zebrafish [4]. In *in vitro* studies BPS is consistently reported to be of similar or slightly weaker potency compared to BPA across more than 24 different studies reporting estrogen receptor activation or antagonism and androgen receptor activation or antagonism [3].

- **Perfluoctanonic acid** (PFOA: 335-67-1): PFOA has a relatively long reported half life of 3.8 years in humans [5] and has numerous endocrine disrupting effects, some of which are highlighted here. PFOA is a thyroid hormone signaling disruptor. A recent systematic review of epidemiological evidence found that childhood exposure was inversely related to serum levels of thyroid stimulating hormone (TSH) in two studies in girls [6]. PFOA also activates the peroxisome proliferator-receptor alpha and disrupts normal mammary gland development, though the mechanism for this disruption is not clear [7]. Another recent systematic review concluded that “PFOA is "known to be toxic" to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species” [8]. PFOA is also of high concern as it was recently “presumed to be an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans” [9]. **We respectfully suggest that Ecology consider expanding this listing to “PFOA and related substances” because there is now evidence [10] that substitutes for PFOA may degrade into PFOA**, and there is a lack of transparency around what these shorter chain substitutes are, as well as data gaps on toxicity and exposure information on them.

- **Tris (1-chloro-2-propyl) phosphate** (TCPP: 13674-84-5): TCPP is known to occur in human milk [11]. TCPP is a pregnane X receptor agonist *in vitro* [12]. TCPP may also disrupt the thyroid hormone signaling system since it altered mRNA expression of phase I and phase II metabolizing enzymes and transthyretin, a protein responsible for transporting the thyroid hormone thyroxine in the blood, as shown in an avian *in vitro* system [13].

- **Tri-n-butyl phosphate** (TNBP: 126-73-8): TNBP antagonizes the androgen and glucocorticoid receptors and is an activator of the pregnane X receptor *in vitro* [12]. TNBP reduced body weight in developmentally exposed F1 female and male rats at 700 or 3000 ppm and 3000 ppm, respectively [14].

- **Triphenyl phosphate** (TPP: 115-86-6): TPP is a developmental and reproductive toxicant in zebrafish, causing reduced fertility, altered vitellogenin expression, altered expression of steroid metabolising genes and steroidogenesis [15-17]. In zebrafish embryos, TPP exposure results in

malformations and disruptions in neurobehavioral endpoints [18-20]. TPP may also be a reproductive toxicant in mice as it reduces body and testis size and decreases expression of testosterone synthesizing genes in males exposed to 300 mg/kg-day for 35 days [21]. In humans TPP in house dust is associated with decreased sperm concentration and altered prolactin levels [22].TPP increases lipid accumulation, pre-adipocyte proliferation and subsequent adipogenic differentiation, and accelerates obesity and development of type II diabetes in rats making it a potential obesogen [23-25]. *In vitro*, TPP is an estrogen receptor alpha, estrogen receptor beta, pregnane X receptor, and peroxisome proliferator-activated receptor gamma agonist and androgen receptor, glucocorticoid receptor, and retinoic acid receptor antagonist [12, 26, 27]. TPP also alters steroidogenesis *in vitro* and alters the expression of thyroid hormone signaling genes [17, 18].

- **Isopropylated triphenyl phosphate** (IPTPP: 68937-41-7): In zebrafish developmental exposure to IPTPP causes disruption of neurobehavioral outcomes [19]. There are also effects in *C. elegans*, specifically reduced differentiation [28]. *In vitro* IPTPP increases progesterone production and decreases gene expression of the steroidogenic enzyme *Hsd3b* [29]. IPTPP also increases lipid accumulation *in vitro,* suggesting it may be obesogenic [23].

- **Tricresyl phosphate** (TCP: 1330-78-5) TCP is a reproductive toxicant in rodents. In rats TCP increases abnormal sperm morphology and ovarian histology and increases serum estradiol concentrations which results in decreased fertility [30-34]. In mice TCP also impairs fertility and causes significant changes in reproductive organ weight and histology [35]. TCP and its metabolite affect Sertoli and Leydig cell function and reduce spermatogonial stem cell viability [36-38]. TCP also causes adrenal lesions [33]. Steroidogenesis is disrupted by TCP *in vitro* and in a zebrafish model [17, 29].

- **Butylated triphenyl phosphate** (TBPP: 78-33-1 & 220352-35-2) TBPP is a reproductive toxicant that disrupts estrous cyclicity in rats, causes ovarian and adrenal lesions, elevated serum estradiol, and decreased fertility resulting in fewer live pups born [32-34].

- **Bis(chloromethyl)propane-1,3-diyl tetrakis-(2-chloroethyl) bis(phosphate)** (V6: 38051-10-4): V6 increases thyroid weight and causes disrupted thyroid histopathology after a 28 day exposure at 600 mg/kg/day and in a two generation reproductive toxicity study [39].

- **Ethylhexyl diphenyl phosphate** (EHDPP: 1241-94-7): In zebrafish EHDPP causes major behavioral disruption after acute exposure and marginal behavioral disruption after developmental exposure [19]. It is of “highest priority” for additional testing due to its performance in a battery of cell based *in vitro* and alternative animal tests for developmental and neurotoxic effects [28]. EHDPP increases basal progesterone production, increases activation of the peroxisome proliferator-activated receptor gamma, and decreases expression of of the steroidogenic enzyme *Hsd3b in vitro* [27, 29].

- **Dipentyl phthalate** (DPP: 131-18-0): DPP is a potent developmental testicular toxicant in rats, having activity at concentrations lower than other phthalate esters [40]. DPP disrupts fetal testosterone production and gene expression levels of the steroid hormone metabolizing enzymes StAR and Cyp11a [40]. DPP also disrupts the retinol signaling pathway *in vitro* [41]. The

retinol signaling pathway directs expression of the Hox genes, the timing of expression of which is essential for proper development.

- **Dicyclohexyl phthalate** (DCHP: 84-61-7): DCHP is antiandrogenic in developing rodents. In rats developmental exposure to DCHP causes several endocrine mediated effects including hypertrophy of thyroidal follicular epithelial cells, increased thyroid weight, reduced prostate weight, atrophy of testicular seminiferous tubules, increased incidence of histopathologic lesions in fetal testis, disrupted Leydig cell aggregation, reduced gene expression of the steroidogenic enzymes *Star*, *Hsd3b1*, and *Hsd17b3*, reduced prepubertal and pubertal testosterone concentrations, reduced male anogenital distance, prolonged preputial separation, and increased male nipple retention [42].[43-48]. Early postnatal exposure to 0.87 nmol DCHP also causes hyperactivity at 4-5 weeks of age [49]. In frogs DCHP causes increased larval mortality and malformations and genome wide changes in xenobiotic metabolism [50]. *In vitro* DCHP is a potential obesogen as it stimulates the glucocorticoid receptor, inhibits the activity of the glucocorticoid homeostasis enzyme 11b-HSD2, causes reduced cortisol secretion in adrenocortical cells, and increases lipid accumulation in differentiating adipocytes [51-54]. DCHP binds to estrogen receptor alpha [55, 56] and induces MCF7 cell proliferation [57, 58]. DCHP is a T3 antagonist and inhibits the expression of thyroid hormone receptor beta [59].

- **Diisobutyl phthalate** (DIBP: 84-69-5): DIBP is antiandrogenic in developing rodents causing numerous reproductive defects. Developmental exposure to DIBP in rats results in decreased male anogenital distance, reduced testicular testosterone production, histopathologic lesions in fetal testis, undescended testes, increased male nipple retention, delayed preputial separation, hypospadias and undescended testes [60-63]. Effects are similar in developmentally exposed mice [64]. In females developmental exposure to DIBP increases anogenital distance, ovarian aromatase gene expression, and ovarian histoarchitectural disarray [65, 66]. DIBP is also potentially obesogenic. Developmental DIBP exposure reduces plasma leptin and insulin levels and gene expression of peroxisome proliferator activated receptor alpha [65]. In zebrafish, DIBP reduces testosterone and alters the gene expression of the steroidogenic enzymes cyp19a, star, and 3bhsd [67]. *In vitro* DIBP decreases testosterone steroidogenesis and is estrogenic in the yeast screen and MCF7 cell proliferation assays [67, 68].

- **Bis (2-ethylhexyl) tetrabromophthalate** (TBPH: 26040-51-7): The metabolite of TBPH, mono-(2-ethyhexyl) tetrabromophthalate (TBMEHP), causes decreased maternal serum T3 and hepatotoxicity, and multinucleated germ cells in fetal testes [69]. TBPH is antiandrogenic and antiestrogenic in *in vitro* yeast screens [70] and causes increased testosterone and estradiol in steroidogenesis assays [70, 71]. TBPH and its metabolite TBMEHP also disrupt *in vitro* metabolism signaling. TBPH induces lipid accumulation *in vitro* [23]. TBPH and TBMEHP are pregnane X receptor agonists while TBMEHP is peroxisome proliferator-activated receptor agonist and TBPH is a pregnane X receptor antagonist [69, 72].

- **Decabromodiphenyl ethane** (DBDPE: 84852-53-9): In rats, DBDPE exposure induces drug-metabolizing CYP enzymes which may have downstream effects on the metabolism of other endogenous hormones [73]. DBDPE also reduces serum T3 [74]. In zebrafish DBDPE reduces the hatching rate and increases hatched larval mortality [75]. *In vitro* DBDPE induces the expression of vitellogenin and is anti-androgenic [75, 76].

2. Support for chemicals submitted for this rule update but not included in the current proposal.

We support the addition of the bisphenols, phthalates, phosphate flame retardants and plasticizers that are listed in the proposed rule amendment. However, there are additional chemicals that should be considered given that they are structurally and functionally similar to those proposed in the amendment and as such are likely to have similar use profiles and possibly biologic impacts following exposure.

It is often the case that when one chemical gains regulatory scrutiny or consumer pressure against it, it is simply replaced with another very similar chemical. This situation makes it increasingly difficult for environmental scientists and consumers to keep up to date with what specific chemical is in any particular consumer product. One solution is to require reporting of all chemicals within a specific chemical structural or use class. Importantly, this should be accomplished by requiring reporting on individual chemicals (i.e. Bisphenol A, Bisphenol S, and Bisphenol F separately, not as total bisphenols), as structurally and/or functionally similar chemicals can have different biological effects. This would help ensure that if manufacturers switch between similar chemicals over time, that there is not a loss of information relevant to hazard assessment.

While there are several chemicals that meet the criteria for inclusion on the CHCC list, we do not desire to hold up the current rule-making process. We appreciate the Department of Ecology's current additions to the list, and look forward to the next opportunity to update the rule with additional chemicals. We are aware, however off additional flame retardants and phthalates that were submitted for consideration of the current rule update but have not been included in the current proposed amendment. **We would like to extend our support for adding them to the current rule amendment. Importantly, these chemicals are known or suspected EDCs.**

- **Diisopentyl phthalate** (DIPP: 605-50-5): Though DIPP is not routinely tested in consumer products, it has been detected in a cosmetic sample, which suggests that it may already be in use on the marketplace [77]. The European Chemicals Agency (ECHA) classifies DIPP as a Category 1A and 1B reproductive toxicant stating that it may impair fertility and harm the unborn child due to its structural similarity to other phthalates, specifically di-n-pentyl phthalate (DNPP) and dibutylphthalate (DBP) [78].

- **Bis(2-methoxyethyl) phthalate** (DEMP: 117-82-8): DEMP and its metabolite methoxyacetic acid (MAA) are developmental toxicants. A single exposure to DEMP on gestational days 10-14 (0.6ml/kg) is embryotoxic causing an increase in the number of resorptions. DEMP is also fetotoxic causing reduced fetal weight and an increase in skeletal and congenital brain malformations [79, 80]. In 10 week old rats a single exposure to 1500 or 2000 mg/kg DEMP decreased testis weight and increased abnormal sperm [81]. Additionally, the metabolite of DEMP, MAA, disrupts early embryo growth and development in culture and is teratogenic *in vivo* [82, 83].

- **Diisooctyl phthalate** (DIOP: 27554-26-3): DIOP has already been detected in some children's' toys [84]. DIOP is a reproductive and developmental toxicant. At higher doses (0.5 and 1 g/kg-day) developmental exposure to DIOP increases resorptions and reduces fetal weight, whereas lower doses (0.1 g/kg-day) reduce testicular testosterone production. Importantly, hypospadias, undescended testes, and skeletal malformations are increased in the offspring of developmentally exposed males [85].

- **Dechlorane Plus** (DP: 13560-89-9): In zebrafish, embryonic exposure to DP causes neurobeavioral defects at non-teratogenic doses [86]. In adult zebrafish, DP causes increased circulating plasma T4 and expression of corticotropin releasing hormone and thyroid stimulating hormone b genes in brain [87].

- **1,2-Bis(2,4,6-tribromophenyoxy)ethane** (BTBPE: 37853-59-1): In humans BTBPE dust concentrations are associated with T3 levels in men [88]. The metabolite of BTBPE, 2,4,6-tribromophenol (2,4,6-TBP) is a thyroid disrupting chemical and bioaccumulates in the placenta [89, 90].

3. We do not support the removal of D4 from the CHCC list.

Octamethylcyclotetrasiloxane (D4; 556-67-2) is used as an intermediate to produce silicone polymers. There have been over 2,300 reports of D4 in children's products to Ecology since 2008, indicating the potential for exposure in children. In Publication No. 17-04-021 Ecology states that "Based on the mixed results on a single assay, there is not sufficient evidence for CSPA of D4 toxicity" [91]. From this, it appears that Ecology has proposed to delist D4 based largely on a 2015 report by Lee et al. that reported that D4 did not induce a uterotrophic response [92]. We do not feel that this is a strong enough rationale for delisting a potentially hazardous EDC. Our reasons are listed below.

- **Despite the lack of a uterotrophic response, Lee et al. (2015) concluded that D4 was estrogenic based on its induction of other estrogen regulated endpoints** *in vivo* and *in vitro* including induction of gene and protein expression of the classic estrogen responsive genes calbindin-D9k (CaBP-9K) and progesterone receptor. The increased expression of CaBP-9K and progesterone receptor was blocked when treatment occurred in the presence of the potent estrogen receptor antagonist ICI 182 780 (ICI), which indicates that D4 was acting through an estrogen receptor mediated mechanism.
- **Earlier studies have all reported that D4 induces a uterotrophic response [93-95].** This finding holds across species (rat and mouse), strains (Sprague Dawley or F-344 rat) and exposure paradigms (oral and inhalation routes; juvenile or ovariectomized adults).
- The *in vivo* study by Lee et al. (2015) is the only study that utilized a subcutaneous route of exposure. It is possible that the route-specific differences in pharmacokinetics of D4 could account for the negative findings in the uterotrophic assay [96].
- Additional support for estrogenic activity is that the uterotrophic response can be blocked by the estrogen receptor specific antagonist ICI [95] and D4 increases epithelial cell height in the uterus, which is another indicator of estrogenic activity [93, 94].
- The potential for estrogenic effects is further supported by the findings of Quinn et al. (2007) and He at al. (2003) who reported binding of D4 to estrogen receptor alpha *in vitro*. Ecology did not acknowledge these findings in document 17-04-021, focusing rather on the lack of binding of D4 to the estrogen receptor in the US EPA's high throughput testing system ToxCast. It has been noted, however, that the negative finding in ToxCast is potentially due to the volatility of D4 and it is possible that "the concentration of the compound actually tested in the high-throughput assays was lower than the calculated nominal concentration" [97].

Upon evaluation of this body of research, we see no reason for the single negative finding in a single assay by Lee et al. to be given more weight than the previous studies in determining the potential toxicity of D4. There is no reason to disregard existing data across species, strains, and

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routes of exposure that indicates that D4 is estrogenic by measurement in the uterotrophic assay, as well as additional *in vivo* and *in vitro* assays.

Perhaps more important, yet not mentioned in document 17-04-021, is that **D4 has consistently been reported to be a reproductive toxicant, causing fetal loss in pregnant rats.** Exposure to D4 causes changes to pregnancy-related hormone concentrations including estradiol, follicle stimulating hormone, and luteinizing hormone [95, 98]. According to the authors of the papers reporting fetal loss [99, 100] the loss is most likely caused by disruption of the luteinizing hormone surge required for ovulation [98, 99]. The suggestion from these papers is that if the pregnancy loss is not a result of D4's estrogenicity, then the fact that D4 is estrogenic can be disregarded. However, regardless of the mechanism, **the fact that D4 caused up to a 38% loss in the number of live pups per litter should not be ignored.** Further, Siddiqui et al. (2007) also reported effects in other estrogen sensitive tissues, such as the mammary gland. Yet Siddiqui et al. (2007) made no attempt to determine the mechanism or the subsequent functional consequences of the mammary gland disruption, which included increased cellular proliferation, secretions, and milk cysts [100]. **Environmental chemicals including EDCs often act on multiple target tissues through more than one mechanism, and it is not necessary to have a fully elucidated mechanism to consider a chemical a potential hazard. D4 clearly has the potential to act as an endocrine disruptor and a reproductive toxicant, as demonstrated by independent academic, government, and industry scientists, and as such, should remain listed on the CHCC under the CSPA.**

Thank you for taking the time to review our comments and please do not hesitate to contact us if you would like further clarification or elaboration on anything we have addressed in our comments.

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