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四溴双酚A (TBBPA)雌性生殖毒性效应及其机制研究进展

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摘　要

四溴双酚A (TBBPA)作为全球使用最广泛的溴代阻燃剂之一，广泛存在于环境介质、生物体甚至人体内，其对女性/雌性生殖健康的潜在威胁已成为环境毒理学研究的热点。本文系统综述了近年来关于TBBPA雌性生殖毒性效应及其作用机制的研究进展。现有研究表明，TBBPA暴露可导致实验动物(如小鼠、大鼠)中卵巢结构损伤、卵泡发育异常、性激素水平紊乱、生育能力下降以及不良妊娠结局等多种负面效应。其毒性机制主要涉及干扰下丘脑－垂体－卵巢(HPO)轴的内分泌调控、诱导氧化应激与细胞凋亡、干扰类固醇激素合成关键酶活性与信号通路等多个层面。然而，关于TBBPA对人类女性生殖健康影响的直接流行病学证据尚不充分，低剂量长期暴露的联合效应及分子机制细节仍需深入探究。未来研究应加强人群暴露评估与健康风险关联分析，并进一步阐明TBBPA与其他环境因素的交互作用，为制定科学的风险评估标准和防控策略提供依据。

关键词

四溴双酚A，雌性生殖毒性，卵巢，内分泌干扰，作用机制

Research Progress on Female Reproductive Toxicity of Tetrabromobisphenol A (TBBPA) and Its Mechanism

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Abstract

As one of the most widely used brominated flame retardants in the world, tetrabromobisphenol A (TBBPA) is widely found in environmental media, organisms and even human bodies. Its potential threat to female/female reproductive health has become a hot topic in environmental toxicology research. This paper systematically reviews the research progress on the female reproductive toxicity of TBBPA and its mechanism in recent years. Existing studies have shown that TBBPA exposure can lead to a variety of negative effects in experimental animals (such as mice and rats), such as ovarian structural damage, abnormal follicular development, disorder of sex hormone levels, decreased fertility, and adverse pregnancy outcomes. Its toxic mechanism mainly involves interfering with the endocrine regulation of the hypothalamus-pituitary-ovary (HPO) axis, inducing oxidative stress and apoptosis, and interfering with the key enzyme activities and signaling pathways of steroid hormone synthesis. However, the direct epidemiological evidence on the effects of TBBPA on human female reproductive health is still insufficient, and the combined effects and molecular mechanism details of low-dose long-term exposure still need to be further explored. Future research should strengthen population exposure assessment and health risk correlation analysis, and further clarify the interaction between TBBPA and other environmental factors, so as to provide a basis for formulating scientific risk assessment standards and prevention and control strategies.

Keywords

Tetrabromobisphenol A, Female Reproductive Toxicity, Ovary, Endocrine Disruption, Mechanism

1. 引言

四溴双酚 A (Tetrabromobisphenol A, TBBPA)作为一种高产量的反应性溴化阻燃剂，广泛应用于电子产品、塑料、纺织品和建筑材料中，以提升产品的防火性能[1]。然而，由于其添加型特性，TBBPA 易从产品中释放，并通过生产、使用、废弃处置等环节进入环境[2]。已在空气、水体、沉积物、土壤以及多种生物体内检测到 TBBPA 及其衍生物的存在[2]-[5]。更值得关注的是，TBBPA 在人体血清、乳汁、脂肪组织以及胎盘等样本中也被频繁检出，例如 2016~2017 年加拿大女性血清中 TBBPA 最大浓度达到 11 ng/g 脂质[6]。人群暴露评估数据显示，普通成人和幼儿通过饮食、饮水及灰尘摄入的 TBBPA 平均每日估计暴露量分别为 0.32 ng/kg/日和 1.2 ng/kg/日[7]，表明不同年龄段人群均存在普遍且持续的暴露[8] [9]。尽管一些研究称 TBBPA 可能是一种安全的化学品，但其具有与双酚 A 相似的结构，已被证实具有内分泌干扰活性，其对甲状腺、神经和生殖系统表现出潜在毒性[2]。此外，国际癌症研究机构(IARC)近期已将其升级为 2A 类(可能对人类致癌)物质[10]，进一步凸显了对其长期健康风险的担忧。女性生殖系统因其对外源性化学物质的高度敏感性而备受关注，TBBPA 的雌性生殖毒性由此成为评估其整体健康风险不可忽视的重要方面。本文旨在系统梳理国内外有关 TBBPA 雌性生殖毒性效应及其内在机制的最新研究进展，以期为全面认识其生殖危害和指导后续深入研究提供参考。

2. TBBPA 的雌性生殖毒性效应

2.1. 对下丘脑–垂体–卵巢(HPO)轴的干扰

动物实验证据表明，四溴双酚 A (TBBPA)及其衍生物 TBBPA-DHEE 均具有明确的生殖内分泌干扰效应。TBBPA 可通过干扰下丘脑–垂体–卵巢(HPO)轴功能，破坏体内性激素稳态。在雌性动物中，TBBPA 暴露可引起血清雌二醇(E2)、孕酮(P4)水平异常，并干扰促卵泡激素(FSH)与促黄体生成素(LH)的分泌节律。研究进一步揭示，TBBPA 能诱导子宫局部 E2 浓度升高，同时显著提升血清及子宫中双酚 A(BPA)水平[11]。其机制可能与促进胎盘细胞系中芳香化酶表达，进而增加 E2 分泌有关[12]。性激素水平的紊乱进而导致动情周期延长、周期不规则甚至中断，反映了 HPO 轴功能失调。

除 TBBPA 外，其衍生物 TBBPA-DHEE 同样表现出显著的神经内分泌干扰潜力。在性发育期斑马鱼中进行为期 40 天的暴露实验发现，TBBPA-DHEE 可干扰下丘脑–垂体–性腺(HPG)轴功能，表现为促性腺激素释放激素(GnRH)、LH 和 FSH 水平显著下降，并伴随行为活动异常，如平均游泳速度和最大加速度下降，社会互动行为降低[13]。这表明 TBBPA-DHEE 能够通过中枢神经内分泌调控途径间接损害生殖功能，进一步揭示了此类污染物对内分泌系统的多层次毒性作用。

综上所述，TBBPA 及其衍生物 TBBPA-DHEE 均可通过干扰 HPO 轴的关键激素分泌与调控，破坏性激素稳态与生殖周期，体现了其在动物模型中明确的生殖内分泌干扰特性。

2.2. 对卵巢的直接毒性(核心靶器官)

动物实验证据表明，四溴双酚 A(TBBPA)及其衍生物在不同物种中均能直接损害雌性生殖系统的结构与功能。在哺乳动物模型中，TBBPA 亚慢性暴露可导致 SD 雌性大鼠卵巢重量及脏器系数改变，并诱发卵巢组织病理学损伤[14]。更为深入的作用机制体现在对卵母细胞成熟的关键干扰。研究表明，TBBPA 能显著损害牛卵母细胞的体外成熟，具体表现为干扰极体挤出与卵丘细胞扩增，诱导减数分裂失败，并伴随纺锤体组装异常和染色体排列错误，最终导致其发育能力与囊胚质量下降[15]。转录组分析进一步从分子层面揭示，TBBPA-DHEE 暴露会下调与卵母细胞减数分裂、成熟及卵巢类固醇生成相关的重要基因(如 cyp11a1、ccna1、ccnb2 等)的表达，从而直接损害卵母细胞的成熟过程[13]。

这种生殖毒性在无脊椎动物中同样得到印证。在以海洋贻贝为模型的研究中，TBBPA 暴露会抑制性腺发育，干扰正常的配子发生过程并降低配子质量[16]。值得注意的是，从哺乳动物到滤食性贝类，TBBPA 均能引发卵泡发育异常、生殖细胞受损等相似表型，这提示其可能通过干扰保守的内分泌轴或细胞发育通路，对不同门类生物的生殖系统产生广泛的负面影响。

2.3. 对生殖道及妊娠维持的影响

TBBPA 对雌性生殖系统的毒性效应不仅局限于卵巢和卵母细胞，更直接延伸至妊娠发生的场所——子宫与胎盘，并最终损害生殖结局。研究显示，即使在环境相关浓度下，TBBPA 仍可诱导小鼠子宫产生显著的病理性损伤，其特征为炎性细胞浸润、促炎因子(如 TNF-α、IL-6)水平升高，并伴随组织水肿与结构破坏[17]。这种炎症微环境的失衡可能为肿瘤发生提供条件：TBBPA 不仅能促进子宫内膜癌细胞增殖与肿瘤生长[18]，长期暴露还可诱导雌性大鼠发生高度恶性的子宫肿瘤，且呈现剂量依赖性[19]。提示子宫是 TBBPA 的易感靶器官，其暴露可能通过激活炎症通路增加子宫癌变风险。

胎盘作为妊娠期间关键的免疫–内分泌界面，同样受到 TBBPA 的损害。TBBPA 可在胎盘细胞系中诱发氧化应激、细胞凋亡并干扰类固醇生成，即使在低浓度(如 10 nM)下亦可检测到凋亡证据，而在较高浓度(20~50 μM)下则显著降低滋养层细胞活力[20] [21]。此外，TBBPA 暴露还能改变胎盘组织中与炎症

反应及神经发育相关生物标志物的表达，进一步破坏胎盘正常功能[22]。

这些对子宫与胎盘的毒性作用最终体现于生殖与妊娠结局的恶化。TBBPA 暴露可降低雌性动物受孕率、延长受孕时间，并导致孕鼠胚胎吸收率增加、活胎数减少、胎仔体重下降及发育迟缓，甚至影响子代性别比例与出生缺陷[23]。值得关注的是，TBBPA 与双酚 A (BPA)相似，均可显著升高妊娠丢失(流产)风险，但二者可能通过差异化的机制扰乱母胎界面免疫微环境——例如以不同方式影响子宫自然杀伤细胞、调节性 T 细胞等关键免疫细胞的数量、比例或功能，从而破坏对胚胎的免疫耐受，最终导致妊娠失败[24]。

综上所述，TBBPA 能够通过损害子宫与胎盘的结构与功能，干扰母胎免疫平衡，系统性地危害雌性生殖健康与妊娠维持。

2.4. 跨代与发育期编程效应

研究发现，TBBPA 的暴露不仅对暴露个体产生直接生殖毒性，更可通过母婴传递与早期暴露，引发显著的跨代健康影响。在人群暴露层面，超过 50%的母乳样本和 30%的母体/脐带血清样本中可检测出 TBBPA，表明母婴在孕期及哺乳期均持续暴露，污染物可通过胎盘与乳汁进入子代体内，进而影响新生儿的生长、发育与行为[8] [19]。孕期作为生理状态剧烈重编程的敏感窗口，母体激素、代谢与免疫系统的变化，连同胎儿快速发育的脆弱性，可能共同导致母胎双方对 TBBPA 等内分泌干扰物的毒代动力学与毒效动力学敏感性显著增强，从而同时威胁母体妊娠结局并干扰胎儿发育编程，产生远期健康风险[25] [26]。

这种跨代传递与早期暴露的生态毒理学意义在鸟类研究中得到进一步阐明。当成年鸟类亲代暴露于 TBBPA 后，污染物可转移并蓄积于所产卵中，直接作用于发育中的胚胎[27]。这种卵内暴露能对子代成年后的生殖功能产生不良影响，在生态层面证实 TBBPA 可通过食物链富集并经卵传递，潜在威胁野生鸟类种群的繁殖成功率。在机制层面，该途径为 TBBPA 的“跨代效应”提供了一种明确的作用模式——即并非通过改变配子的表观遗传信息，而是通过胚胎期的直接毒性暴露，编程子代成年后的生殖系统功能。综上，TBBPA 的跨代毒性既体现在人类母婴传递所致的早期暴露与健康风险，也体现在野生动物经卵传递引起的种群级生殖损害，凸显其作为持久性内分泌干扰物的广泛生态与健康威胁。

3. TBBPA 雌性生殖毒性的作用机制

3.1. 内分泌干扰作用

TBBPA 作为一种典型的内分泌干扰物(EDCs)，其雌性生殖毒性的核心机制在于能够模拟或干扰天然激素的合成、转运、结合及代谢过程，从而破坏生殖内分泌稳态[28]。这种效应主要源自 TBBPA 作为广谱配体，与多种核受体及代谢酶发生直接相互作用。在甲状腺激素系统中，TBBPA 因结构类似甲状腺激素(T4)，可与人转甲状腺素(TTR)竞争性结合，且结合能力较 T4 强 10.6 倍，显著干扰甲状腺激素的转运与代谢，进而影响该通路在雌性生殖发育与功能调节中的正常作用[29]-[31]。

在性激素系统方面，TBBPA 表现出明确的雌激素活性，其通过结构中的酚羟基与雌激素受体(ER)结合，模拟天然雌激素 17β-雌二醇的作用，激活 ER 信号通路，促进雌激素依赖性细胞(MtT/E-2)的增殖和基因表达，但其效力通常低于非溴化类似物双酚 A (BPA) [32] [33]。研究进一步显示，在雌性小鼠中，TBBPA 暴露可能通过竞争性抑制 UDP-葡萄糖醛酸转移酶(UGT)、雌激素磺基转移酶(SULT)等关键代谢酶，导致 BPA 和雌二醇在雌性小鼠体内滞留时间延长、浓度升高，进而增强其潜在的雌激素效应及生殖毒性[11]。此外，TBBPA 及其硫酸盐结合物还能激活过氧化物酶体增殖物激活受体 γ (PPARγ)，该通路与脂质代谢及细胞分化调控密切相关[34] [35]。

除受体介导的途径外，TBBPA 还可直接抑制激素代谢酶的活性。研究表明，TBBPA 在体外能抑制雌二醇的硫酸化过程，最新证据进一步揭示其可通过高亲和力结合雌激素磺基转移酶(SULT1E1)，从酶活性层面延长内源性雌激素的生物效应[29] [36]。综上所述，TBBPA 通过多靶点干扰甲状腺激素与性激素的受体结合、转运及代谢清除，构成其破坏内分泌稳态、进而引发下游生殖毒性的关键分子机制。

3.2. 诱导氧化应激与细胞凋亡

氧化应激是 TBBPA 诱导雌性生殖毒性的关键保守机制之一，其核心在于通过干扰细胞内氧化还原稳态，引发广泛的分子与细胞器损伤。TBBPA 可导致活性氧(ROS)水平异常升高，进而诱发脂质过氧化、蛋白质及 DNA 氧化损伤，最终破坏生殖细胞的发育与功能[37] [38]。这一过程在多种生物模型中均得到证实：在哺乳动物、鱼类乃至海洋贻贝(Mytilus galloprovincialis)中，TBBPA 暴露均能诱发显著的氧化应激反应，表现为 ROS 积累、抗氧化酶(如 SOD、CAT)系统失衡及脂质过氧化标志物增加[15] [16] [39]。

线粒体作为 ROS 产生的主要场所和细胞能量代谢中心，是 TBBPA 生殖毒性的早期敏感靶点。研究表明，TBBPA 可严重损害线粒体结构与功能，导致线粒体膜电位下降、ATP 合成不足及线粒体 DNA 拷贝数减少，并诱导线粒体源性 ROS 爆发[28] [40]-[43]。在牛卵母细胞这一典型模型中，TBBPA 通过调控丙酮酸脱氢激酶 3 (PDK3)的表达，破坏线粒体能量代谢与氧化平衡，进而引起纺锤体组装异常、染色体排列错误以及早期细胞凋亡，最终损害卵母细胞的核质成熟与发育潜力[15]。类似地，在日本虎斑猛水蚤中，高浓度 TBBPA 暴露导致卵母细胞线粒体嵴溶解，ROS 大量释放，破坏卵黄膜与卵黄颗粒完整性，影响卵母细胞成熟[27]。

综上所述，TBBPA 通过破坏线粒体功能、诱发氧化应激并削弱细胞抗氧化防御，从能量代谢、氧化平衡及细胞器完整性等多个层面协同损害雌性生殖细胞质量与胚胎发育，这构成了其生殖毒性的共性分子基础。

3.3. 对信号通路的干扰

TBBPA 可通过干扰多种保守的细胞信号通路，系统地影响雌性生殖内分泌调节、代谢稳态及肿瘤抑制网络，从而介导其生殖毒性。在无脊椎动物模型中，TBBPA 暴露能广泛影响与类固醇激素合成、脂质代谢及炎症相关的生物过程。例如，在紫贻贝中，TBBPA 可上调酯酰辅酶 A 氧化酶(ACOX1、ACOX3)及 CYP2U1 等基因的表达，促进脂肪酸 β-氧化与花生四烯酸代谢，从而干扰脂质平衡并对生殖内分泌系统产生毒性效应[44]。在海洋青鳉中，TBBPA 不仅改变下丘脑–垂体–甲状腺轴(HPT)与生长激素/胰岛素样生长因子(GH/IGF)轴相关基因表达，还会引发内质网应激，这可能解释其跨代发育异常现象[45]。

在核受体层面，TBBPA 可通过结合雌激素受体(ER)、雄激素受体(AR)等干扰下游靶基因转录，影响性腺发育与配子形成[33]。此外，TBBPA 还能通过非受体途径直接破坏关键的细胞调控网络。研究显示，TBBPA 可通过促进 p53 蛋白的泛素化降解，削弱这一核心肿瘤抑制因子的功能，从而显著增强子宫内膜癌细胞的增殖与成瘤能力，揭示了一条独立于经典激素受体的致癌通路[18]。与此同时，在子宫组织中，TBBPA 可通过抑制甲状腺激素受体 β (THRβ)的表达，进而激活 PI3K/NF-κB 炎症信号通路，打破局部免疫平衡，诱发慢性炎症微环境[17]。这种对肿瘤抑制通路与免疫–炎症通路的双重干扰，表明 TBBPA 可能通过多机制协同促进子宫病理损伤甚至癌变。

综上，TBBPA 的雌性生殖毒性涉及对代谢、内分泌、炎症及肿瘤抑制等多条信号网络的广泛干扰，这些通路间的交叉对话可能共同放大了其生物学效应，在全面评估其健康风险时必须予以综合考量。

3.4. 基于混合暴露的复合毒性机制

如前所述，TBBPA 可通过干扰内分泌、诱导氧化应激及调控信号通路等多种途径发挥雌性生殖毒性。

然而，现实环境中 TBBPA 常与双酚 A (BPA)、重金属(如镉 Cd、铅 Pb)及微塑料等共存于电子垃圾拆解区及室内灰尘中，构成复杂的混合暴露场景[46]-[48]。这种联合暴露可能通过影响毒代动力学与毒效动力学两条途径产生协同或拮抗效应，使其对雌性生殖系统的毒性较单一暴露更为复杂。在毒代动力学层面，TBBPA 与 BPA 共享葡萄糖醛酸转移酶(UGT)和磺基转移酶(SULT)代谢途径，TBBPA 可通过竞争性抑制这些代谢酶的活性，减缓 BPA 的清除，从而显著提高 BPA 在子宫和卵巢等生殖器官中的蓄积浓度，间接增强其雌激素样效应[11]。在毒效动力学层面，TBBPA 与重金属的联合暴露常表现为协同诱导氧化应激与细胞凋亡。例如，TBBPA 与 Cd 在电子垃圾回收场地周围环境介质中广泛共存[49] [50]，亚慢性毒性实验显示，Cd 与 TBBPA 联合暴露可加重青春期雌性大鼠的卵巢损伤，联合暴露组卵巢重量下降幅度(20.8%)较单独 Cd 组(32.4%)更为明显，并显著干扰 SOD 活性和升高 MDA 水平，表现出氧化应激的交互作用，进而对卵巢颗粒细胞功能和卵泡发育微环境构成威胁[14]。类似地，TBBPA 与 Pb 的联合暴露可通过协同激活 JAK2/STAT3 信号通路，加剧线粒体膜电位丧失及 Caspase3/9 活化，诱导比单一暴露更严重的细胞凋亡[48]。此外，TBBPA 与聚苯乙烯纳米塑料或聚乙烯微塑料的联合暴露亦可通过诱导氧化应激、阻滞细胞周期及增加 LDH 活性，产生协同细胞毒性[51] [52]。综上，TBBPA 在混合暴露场景下可通过干扰共污染物的体内代谢过程或协同激活氧化损伤与凋亡通路，从而放大其生殖毒性效应。

4. 总结与展望

现有研究充分证实，TBBPA 对雌性生殖系统具有多方面的毒性效应，贯穿整个生殖轴，并可能产生跨代影响。其机制是网络化的，涉及内分泌干扰、氧化损伤、细胞凋亡及信号通路紊乱等多个复杂且相互关联的层面。然而，目前研究仍存在一些不足：多数毒理学数据来自高剂量动物实验，与环境相关低剂量长期暴露的真实风险评估存在差距；对 TBBPA 代谢产物(如 TBBPA 衍生物、脱溴产物)的生殖毒性研究相对薄弱；关于 TBBPA 与其他环境污染物(如其他 EDCs、重金属)的联合生殖毒性亟待探索；人群流行病学研究稀缺，难以建立确切的暴露–反应关系。

未来可开展更符合真实环境暴露场景的低剂量、长期、多代生殖毒性研究，加强 TBBPA 及其代谢产物在生殖系统中的毒代动力学研究，利用组学技术(转录组、蛋白组、代谢组、表观基因组)系统揭示其毒性网络，推进基于人群的队列研究或病例对照研究，明确 TBBPA 暴露与女性不孕、卵巢功能早衰、不良妊娠结局等生殖健康问题的关联，探讨有效的干预措施(如抗氧化剂)以缓解其生殖毒性。深化对 TBBPA 雌性生殖毒性及其机制的认识，对于保护女性生殖健康、制定科学的环境质量标准与公共卫生政策具有重要意义。

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