Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 706-717 | ISSN:2251-6727

Ecotoxicological Assessment of Synthetic Fragrance Compounds as Endocrine Disruptors in Freshwater and Marine Vertebrates: An overview

Sompalli Bhavana[1]* and Pooja R[2]

[1,2]Assistant Professor, Department of Biotechnology, Surana College Autonomous, Southend Road, Bangalore-560004

(Received: 27 September 2025 Revised: 05 October 2025 Accepted: 10 November 2025)

KEYWORDS

Synthetic Musks, Endocrine Disruption, Aquatic Contamination, Galaxolide (HHCB), Wastewater Effluent, Hormonal Pathways

ABSTRACT:

Synthetic fragrance compounds, widely employed in household and personal care products, have become persistent pollutants in aquatic ecosystems due to insufficient removal during wastewater treatment processes. This review highlights their capacity as endocrine-disrupting chemicals (EDCs) on aquatic animals. Principal scent compounds, such as galaxolide (HHCB), tonalide (AHTN), and musk ketone, were identified in wastewater effluents and surface waters at quantities varying from nanograms (ng/L) to micrograms (µg/L). This paper elucidates the mechanisms of hormonal interference in fish and amphibians, focusing on estrogenic, androgenic, and thyroidal pathways, through a synthesis of literature, experimental design, and in silico toxicity modeling. The findings suggest that extended, low-level exposure to these chemicals can alter reproductive behavior, gonadal development, and endocrine gene expression. Combining analytical chemistry, molecular assays, and ecological modeling is crucial for evaluating the cumulative danger of fragrance-derived endocrine-disrupting chemicals and formulating mitigation methods for sustainable aquatic ecosystem health.

Introduction

The ongoing and extensive production and application of chemicals throughout the last hundred years have led to the constant release of various synthetic organic compounds, frequently found in household, cosmetic, and personal care products, into the worldwide ecosystem. A notable subset in this category comprises the Pseudo-Persistent Organic Pollutants (P-POPs), distinguished by their ongoing release that sustains a persistent environmental concentration, despite relatively short half-lives [1]. This situation renders aquatic habitats—the ultimate recipients of urban and industrial discharges—especially susceptible. A good example is the group of synthetic scent chemicals, or musk-like substances, that are used all over the world to make many consumer products smell better [2]. As a result, treated wastewater effluent acts as a primary and ongoing pathway for the direct introduction of these musks into rivers, lakes, and coastal waters, thereby categorizing them as enduring pollutants within the aquatic ecosystem. The levels of wastewater discharges like Galaxolide (HHCB), Tonalide (AHTN), and Musk Ketone (MK) are usually high nanograms per liter (ng/L) to low micrograms per liter (µg/L) [3]. The observed ambient concentrations hold considerable significance from an ecotoxicological perspective. The elevated log K_{ow} values of these musks enhance their bioaccumulation in the tissues of aquatic organisms, which may result in internal concentrations surpassing those found in the surrounding water, thereby ensuring chronic, lifelong exposure to intricate chemical mixtures [4].

The primary ecological concern centers on the role of synthetic musks as Endocrine-Disrupting Chemicals (EDCs). EDCs are external substances that alter the endocrine system, leading to negative health effects on an organism, its progeny, or particular populations. Aquatic vertebrates, such as fish and amphibians, serve as highly sensitive indicators of this disruption, given that hormonal signals closely regulate their life cycles [5]. Literature and in silico evidence strongly indicate that these synthetic musks are not simply inert contaminants; rather, they have molecular structures that can interact with hormone receptors or steroidogenesis enzymes, thus disrupting estrogenic, androgenic, and thyroidal pathways. Given the documented environmental presence of HHCB, AHTN, and MK, and the increasing toxicological evidence, researchers must conduct a comprehensive examination of the specific

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 706-717 | ISSN:2251-6727

effects of notable concentrations ranging from (ng/L) to (µg/L) on aquatic vertebrates [6].

This study combines a thorough review of existing literature and toxicological data and an experimental approach with model aquatic organisms to evaluate the effects of relevant concentrations on biological outcomes. Additionally, in silico toxicity modeling is employed to predict the molecular mechanisms of action, with a particular emphasis on the binding affinity and agonistic/antagonistic activity associated with critical nuclear receptors, including the estrogen receptors (ERα) and androgen receptors (AR). The main objective is to clarify the mechanistic links between extended, low-level exposure to synthetic musks and the adverse effects observed in fish and amphibians. Key endpoints include changes in reproductive behavior, histological signs of disrupted gonadal development, and alterations in the expression of crucial endocrine-related genes. The results underscore the essential requirement to move towards a thorough risk assessment framework that seamlessly incorporates analytical chemistry for exposure evaluation, molecular assays for understanding mechanisms, and ecological modeling for precise assessment and prediction of health impacts on global aquatic ecosystems.

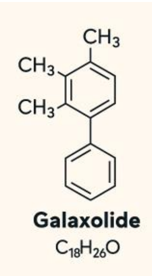
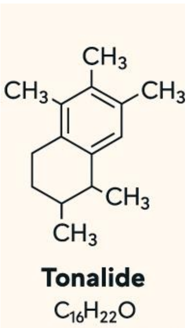
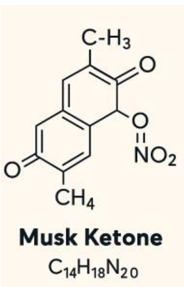
Sources and Environmental Distribution of the Synthetic Musks

The extensive use of synthetic musks and other fragrance compounds in cosmetics and detergents results in a continuous influx into wastewater systems. Traditional wastewater treatment facilities (WWTPs) exhibit limitations in effectively eliminating these compounds, attributed to their hydrophobic and enduring characteristics, thereby reinforcing their classification as Pseudo-Persistent Organic Pollutants (P-POPs)[7].

The efficiency of conventional wastewater treatment plants varies significantly and is influenced by the structural characteristics of specific compounds as well as the operational parameters of the facility, such as sludge retention time. Sorption onto sludge biomass primarily facilitates removal, not complete biodegradation. Given their significant lipophilicity log K_{ow} (5.7–5.9), these musks partition onto activated sludge and accumulate in various environmental matrices, such as sediments and the tissues of aquatic organisms [8]. Bioaccumulation has been extensively documented in fish, particularly in lipid-rich organs such as the liver and gonads, as well as in mussels, where tissue concentrations can sometimes be attained. The wet weight is measured in mg/kg. Importantly, metabolites such as HHCB-lactone frequently exhibit enhanced persistence and can play a substantial role in the overall toxic load [9].

The remaining quantities released into aquatic environments build up in sediments and living organisms, resulting in prolonged exposure for aquatic life. Bioaccumulation has been reliably observed in fish tissues, particularly in lipid-rich organs like the liver and gonads, where levels are elevated. The elevated log K_{ow} values (e.g., HHCB ≈ 5.9, AHTN ≈ 5.7) indicate a significant propensity for partitioning into organic phases, such as sludge and biological lipids[10]. Concentrations in fish and mussels have been documented to reach up to the mg/kg wet weight range, which is comparable to or even exceeds levels of some regulated Persistent Organic Pollutants (POPs) in specific areas [11]. Recent findings suggest that musk metabolites, including HHCB-lactone, may exhibit greater environmental persistence and toxicity compared to their parent compounds, thereby contributing substantially to the overall toxic burden within biota. The limited biomagnification of synthetic musks is noteworthy. Although bioaccumulation from water and sediment is considerable, research indicates that these compounds show minimal biomagnification. Biomagnification occurs because higher-trophic-level organisms, such as fish, possess the metabolic ability to process and eliminate toxins effectively. Nonetheless, the phenomenon varies by species[12,13].

Table 1: Environmental Occurrence and Fate of Synthetic Fragrance Compounds in Wastewater and Aquatic Systems.

Compound	Common Use	WWTP Removal Efficiency	Typical Environmental Concentration	Fate of the contaminant	References
Galaxolide (HHCB) 	Perfume, detergents	60–80%	50–800 ng/L	The presence of metabolite HHCB-lactone in effluent frequently exceeds that of the parent compound, presenting a unique and enduring risk.	[14]
Tonalide (AHTN) 	Cosmetics, air fresheners	50–75%	20–500 ng/L	Tonalide (AHTN) typically demonstrates a lower reactivity to advanced oxidation processes, such as ozone, than HHCB.	[15]
Musk ketone (MK) 	Soaps, lotions	40–60%	10–200 ng/L	Usage is limited in numerous areas due to increased apprehensions about persistence and toxicity in comparison to polycyclic musks.	[16]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 706-717 | ISSN:2251-6727

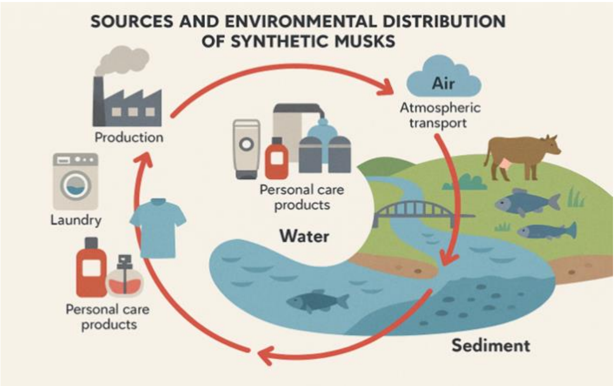


Fig 1: Various sources and environmental distribution of synthetic musks affecting biota

Mechanisms of Endocrine Disruption

Estrogenic Effects (Xenoestrogenicity):

Synthetic musks function as xenoestrogens and anti-androgens, disrupting the vertebrate hypothalamic-pituitary-gonadal (HPG) axis. This dual interference plays a vital role in reproductive function. Synthetic musks, especially the polycyclic types such as HHCB and AHTN, exhibit a weak yet detectable affinity for estrogen receptors (ERα and ERβ) [17]. Although their binding affinity is frequently much lower than that of the natural ligand (17β-estradiol), their persistent and high-volume occurrence in aquatic environments indicates that the overall environmental burden can be considerable. This type of receptor is the most common biomarker for environmental factors[18]. Investigations involving zebrafish (Danio rerio) and Japanese medaka (Oryzias latipes) have consistently demonstrated that exposure to environmentally relevant levels of HHCB and AHTN results in measurable VTG synthesis in male fish. This molecular feminization indicates a disruption in functionality[19]. Prolonged exposure has been associated with histological alterations in the gonads of affected fish, such as the emergence of intersex traits (testis-ova) and diminished fertility. This disruption is related to the estrogen signaling pathway. Estrogenicity refers to the induction of vitellogenin (VTG), a yolk precursor protein that is typically produced solely by female fish during their reproductive cycles[20].

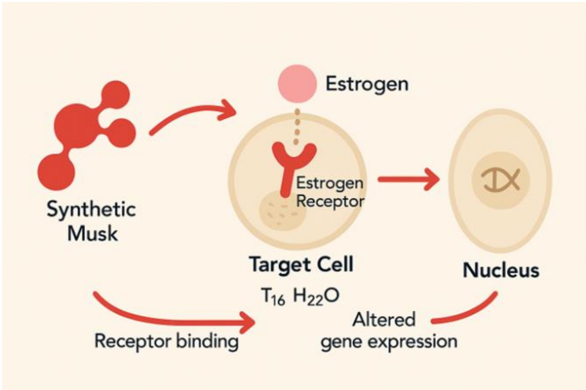


Fig 2: Estrogenic Effects (Xenoestrogenicity) of synthetic musks in Aquatic Mammals

Anti-Androgenic Effects

Synthetic musks disrupt male hormone signaling by functioning as antagonists to the androgen receptor (AR). These substances compete with natural androgens, such as testosterone and 11-ketotestosterone, for binding to the androgen receptor, thereby inhibiting the downstream androgenic signaling essential for male development and function[21]. Studies show that polycyclic musks can hinder essential enzymes involved in steroidogenesis, specifically 17β-hydroxysteroid dehydrogenase (17β -HSD) and cytochrome P450 side-chain cleavage enzyme (P450 scc), resulting in decreased circulating testosterone levels[22]. In fish, androgen signaling regulates the development of male secondary sexual characteristics, such as breeding tubercles and fin morphology. Exposure to HHCB and AHTN has demonstrated an impact on the demasculinization of these traits, influencing mating success and reproductive behavior[23,24].

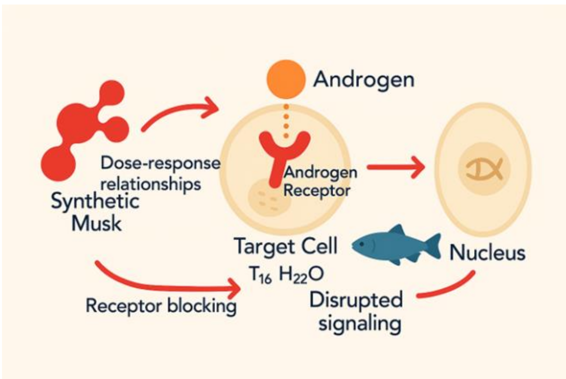


Fig 3: Anti-Androgenic Effects of synthetic musks in Aquatic Mammals

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 706-717 | ISSN:2251-6727

Thyroid Hormone Disruption

Thyroid hormones play a vital role in regulating metabolism, supporting growth, and facilitating metamorphosis in amphibians. Synthetic musks are increasingly recognized as significant disruptors of the thyroid system. The active thyroid hormone, triiodothyronine (T3), is mainly synthesized in target tissues through the conversion of circulating thyroxine (T4) by deiodinase enzymes (D1, D2, D3) [25]. Fragrance compounds have been observed to inhibit deiodinase activity. By inhibiting this conversion, musks significantly lower the levels of T3 that are essential for triggering important developmental processes. Certain musks may also vie with T4 for attachment to transthyretin (TTR), a protein responsible for plasma transport. This competition has the potential to change the overall distribution and availability of T4 within the body [26]. The African clawed frog exemplifies the amphibian model. Exposure to HHCB and AHTN at sublethal concentrations leads to significant developmental delays, such as delayed metamorphosis, abnormal limb development, and skeletal deformities. This effect results directly from inadequate T3 signaling. *Xenopus laevis* offers distinct and quantifiable indicators for assessing thyroid disruption [27]. Recent studies have validated changes induced by musk in the expression of genes associated with the thyroid, such as the thyroid hormone receptor-β and T3 target genes, in tadpoles [28].

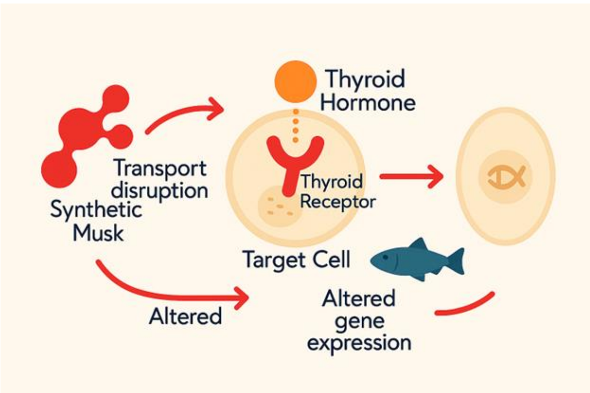


Fig 4: Thyroid Hormone Disruption of Synthetic Musks in Aquatic Mammals

Genomic and Epigenetic Alterations

The most significant adverse effects arise from the disruption of gene expression induced by musk and potentially epigenetic programming, which regulates persistent heritable modifications. Aromatase (CYP19A1) is an enzyme that facilitates the transformation of androgens into estrogens. The altered expression of CYP19A1 serves as a significant indicator of exposure to EDCs. Exposure to HHCB and AHTN has been shown to increase the production of estrogen in the brain and gonads of fish by up-regulating CYP19A1. This is linked to feminization and endocrine disruption [29,30].

Transcriptomic studies consistently indicate changes in the expression of genes that encode ERβ. Genes that encode ER are often modified as a compensatory mechanism in response to xenoestrogen interaction[31]. Vitellogenin (VTG) has been observed to have transcription that is significantly activated in males, and in the case of Peroxisome Proliferator-Activated Receptors (PPARs), research indicates that polycyclic musks can activate PPARs, which play a crucial role in regulating lipid metabolism. This connection suggests that exposure to musks may lead to potential metabolic disruptions in addition to endocrine effects [32].

Epigenetic mechanisms

Epigenetics involves inheritable modifications in gene activity that take place without altering the DNA sequence itself. The addition of a methyl group to DNA, known as DNA methylation, serves as a crucial epigenetic mark that generally leads to the silencing of gene expression[33]. Recent studies indicate that prolonged or early-life exposure to synthetic musks may lead to alterations in DNA methylation within the germline (sperm/oocytes) and somatic tissues of affected organisms. These alterations frequently focus on the promoter regions of essential endocrine genes, such as those within the HPG axis[34]. This epigenetic reprogramming serves as a mechanism that underpins transgenerational effects, specifically the adverse outcomes seen in unexposed offspring. This phenomenon may elucidate the long-term reproductive impairments and the population-level consequences observed in ecological models[35].

Toxicological Evidence in Aquatic Vertebrates

Synthetic fragrance compounds demonstrate a variety of toxic effects in aquatic vertebrates, encompassing endocrine disruption, reproductive toxicity, developmental delays, and genotoxicity. Their

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 706-717 | ISSN:2251-6727


hydrophobic and lipophilic properties promote bioaccumulation in tissues like the liver, gonads, and brain, leading to chronic sublethal effects that hinder population fitness[36,37].

Table 2: Toxicological Responses of Aquatic Vertebrates to Synthetic Fragrance Compounds

Species	**Chemical**	**Concentration/Duration**	**Observed Effects**	**Reference**
Danio rerio (Zebrafish)	Galaxolide (HHCB)	500 ng/L, 30 d	↑ Vitellogenin, testicular atrophy	[38]
Oryzias latipes (Medaka)	Tonalide (AHTN)	200 ng/L, 21 d	↓ Egg output, feminization	[39]
Xenopus laevis (Amphibian)	Musk ketone	100 ng/L, 30 d	Delayed metamorphosis, thyroid disruption	[25]
Cyprinus carpio (Carp)	Galaxolide	Field exposure	Hepatic accumulation alters CYP activity.	[40]
Oncorhynchus mykiss (Trout)	Tonalide	1 µg/L, 14 d	DNA damage, micronuclei formation	[41]

Analyses of toxicogenomics indicate notable disruptions in transcriptional and enzymatic activities: The reduction of androgen receptor (AR) and 17-hydroxysteroid dehydrogenase negatively affects steroidogenesis[42]. The activation of cytochrome P450 aromatase (CYP19A1) and vitellogenin (Vtg) genes results in the feminization of males. The inhibition of deiodinase (DIO1 and DIO2) enzymes leads to the disruption of T4–T3 conversion and thyroid homeostasis[43]. Increased levels of oxidative stress indicators (superoxide dismutase, catalase, and lipid peroxidation) imply the presence of secondary oxidative damage processes. Proteomic studies indicate alterations in plasma proteins linked to lipid transport and reproduction, suggesting a broader metabolic disruption within the system[44].

Analytical and Detection Methods: Merging Sophisticated Analytical Techniques and Bio-Effect Instruments for Evaluating Synthetic Musk Risks

The modern methodology for evaluating the ecotoxicological risks associated with synthetic musk fragrances (SMFs) in environmental matrices has developed into a robust, integrated system that merges ultra-sensitive chemical detection with functional biological screening and predictive computational models [45]. Gas Chromatography–Mass Spectrometry (GC–MS) and Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS) continue to serve as foundational analytical techniques. Recent developments, including the implementation of GC–Triple Quadrupole MS/MS (GC–QqQ–MS/MS) in Multiple Reaction Monitoring (MRM) mode, facilitate

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 706-717 | ISSN:2251-6727

the precise quantification of lipophilic polycyclic musks (HHCB, AHTN) and their significant metabolites (e.g., HHCB-lactone) at concentrations ranging from (ng/L) to (pg/L) in complex matrices such as wastewater effluents, fish tissue, and sediments [46]. The improved sensitivity and selectivity are essential for addressing matrix effects, especially in the analysis of fish samples with elevated lipid levels or sediments that necessitate intricate extraction techniques such as Accelerated Solvent Extraction (ASE) or Solid-Phase Microextraction (SPME) [47]. At the same time, high-resolution mass spectrometry (HRMS) is becoming increasingly prominent, providing exceptional mass accuracy that allows for the reliable differentiation of SMFs from overlapping interferences, which poses a considerable challenge in environmental monitoring. In addition to identifying chemicals, bioassays offer a crucial functional assessment of toxicity [48]. The Yeast estrogen screen (YES) and the E-screen assay (utilizing MCF-7 cells) serve as established methods for efficiently evaluating samples, measuring the overall estrogenic activity of the complete chemical mixture—not limited to the specific musks—and translating it into 17β-Estradiol Equivalents (EEQ) [49]. Research demonstrates that musks and their degradation products activate estrogen receptor-mediated proliferation in these assays, thereby validating their classification as Endocrine-Disrupting Chemicals (EDCs), albeit generally exhibiting weak effects. To facilitate resource-intensive experimental work, computational toxicology utilizes quantitative structure-activity relationship (QSAR) models and in silico molecular docking [50]. QSAR models predict physicochemical characteristics, including bioaccumulation potential and toxicological endpoints. In contrast, docking studies utilize 3D structural data on receptors (ER, AR) to estimate the binding affinity of new or untested musks, allowing for the prioritization of compounds that pose the greatest inherent hazard for subsequent biological testing [51]. The Integration of Chemical and Biological Detection (ICBD)—analyzing the predicted biological effect derived from quantified concentrations against the actual effect observed through bioassays—offers a thorough understanding of risk. This approach guarantees that both recognized contaminants and the "unknown toxic burden" of complex mixtures are considered in a comprehensive, effect-based evaluation of aquatic ecosystem health [52].

Ecological and Regulatory Implications

The release of persistent and bioaccumulative synthetic musk fragrances (SMFs) into the environment presents serious ecological implications that extend beyond isolated physiological impacts, endangering the stability of ecosystems [53]. Recent research demonstrates that the endocrine-disrupting and toxic properties of musks, such as Galaxolide (HHCB) and Tonalide (AHTN), result in reproductive dysfunction in aquatic organisms, including fish and amphibians [54]. Over time, such impacts can diminish population resilience and significantly alter trophic interactions, such as influencing the foraging behavior of predators or impacting the overall health of microbial communities essential for nutrient cycling. Despite the accumulating evidence, which includes the detection of HHCB and AHTN at high-risk quotients (RQ>1) near wastewater treatment plant (WWTP) discharge sites, SMFs have not yet been universally classified as priority pollutants in numerous global regulatory frameworks[55]. This situation highlights a significant monitoring gap that is currently being addressed by the scientific community. Addressing this pervasive pollution necessitates a comprehensive approach centered on controlling sources and advancing technological solutions[56]. The fragrance industry is experiencing a significant transition towards sustainable practices, emphasizing the preference for macrocyclic and alicyclic musks instead of the more enduring polycyclic and nitro musks[57]. This method entails employing biocatalysis and more sustainable synthesis pathways to develop readily biodegradable alternatives, tackling the issue directly at the point of production. At the same time, enhanced oversight measures should be implemented alongside advanced oxidation processes (AOPs) in wastewater treatment plants (WWTPs)[58]. Studies conducted in 2023-2024 have demonstrated that while traditional treatment methods fall short, advanced treatments such as ozonation and UV-based AOPs (e.g., UV/H or UV/FAC) can effectively eliminate over 90% of most musks by producing highly reactive hydroxyl radicals (OH). Nevertheless, specific compounds, such as musk ketone, persist in exhibiting partial resistance. The comprehensive implementation of these eco-friendly chemical alternatives and cutting-edge wastewater technologies is crucial for alleviating environmental impacts and protecting aquatic ecosystems from these emerging pollutants[59,60].

Future scope

The future direction of studies on fragrance compounds is shifting towards a more comprehensive, mechanism-oriented, and predictive approach to risk assessment, driven by the shortcomings of conventional single-chemical, acute-exposure toxicology. To comprehend the cumulative, hereditary effects of prolonged, low-level exposure, it is imperative to concentrate on chronic, multi-generational studies [61]. Recent research on other endocrine-disrupting chemicals (EDCs) has demonstrated a heightened, cumulative incidence of diseases, such as obesity, in subsequent generations that were not directly exposed. Persistent synthetic musks are likely to be relevant to this finding [62]. To elucidate the intricate biological pathways of disruption, multi-omics approaches—combining transcriptomics, metabolomics, and proteomics—are essential. The incorporation of these high-throughput technologies, as demonstrated in 2024 studies on various EDCs, is crucial for uncovering subtle synergistic effects and identifying the precise molecular pathways (e.g., disruption of the TORC1 signaling pathway or metabolic cycles) through which musks influence cellular function and hormone regulation [63,64]. At the same time, the development of advanced wastewater treatment technologies needs to speed up the pace of innovation in getting rid of these common pollutants. Ozonation and UV-based advanced oxidation processes (AOPs) demonstrate significant removal rates[65]. Ongoing investigations aim to enhance their sustainability and effectiveness by incorporating photocatalysis with innovative visible light-responsive catalysts, as well as refining biofiltration and membrane bioreactors to address recalcitrant compounds. Ultimately, to connect laboratory discoveries with practical environmental management, ecological modeling plays a crucial role [66]. The sophisticated population models, which extend past basic risk characterization ratios (RCRs), are capable of incorporating individual-level effects (such as decreased fecundity) alongside ecological dynamics (including population density and recovery potential) to effectively forecast long-term population-level outcomes, thus equipping managers with evidence-based decision-making frameworks [67]. To achieve these objectives, it is crucial to promote interdisciplinary collaboration among toxicologists, environmental chemists, engineers, and ecologists. This collaboration is crucial for creating genuinely sustainable, safe, and effective solutions that span from the chemical synthesis phase to environmental remediation.

Emerging Environmental Concerns and Global Outlook

Despite significant progress in analytical detection and regulation, synthetic musks continue to pose emerging challenges at the global scale. Their widespread use in personal care and household products ensures a constant influx into aquatic environments, where they resist degradation and accumulate in sediments and biota. Seasonal variations in wastewater discharge and urban runoff further complicate their environmental distribution, often leading to elevated concentrations during dry seasons. The persistence of these compounds across environmental compartments raises concerns about long-term ecological resilience, especially in sensitive ecosystems such as estuaries and wetlands that act as biological filters. Addressing these emerging concerns requires continuous global cooperation, harmonized monitoring protocols, and public awareness initiatives to minimize their uncontrolled release.

Conclusion

The widespread presence of persistent, bioaccumulative synthetic fragrance compounds in aquatic ecosystems represents a significant and frequently neglected ecotoxicological risk, demanding immediate global attention to water management and chemical regulations. The chemicals in question, primarily released through wastewater, act as powerful endocrine disruptors, as evidenced by recent studies that demonstrate their ability to disrupt the hormonal systems of fish and amphibians by mimicking or blocking estrogen and androgen receptors. This hormonal interference results in significant reproductive and developmental issues, including the feminization of male fish and decreased fertility, which ultimately jeopardize the stability and biodiversity of entire aquatic populations. Confronting this crisis requires a comprehensive approach: establishing more stringent, evidence-based regulatory frameworks that consider non-monotonic effects and chemical combinations; promoting innovation in green chemistry to create inherently safer, non-persistent macrocyclic and alicyclic substitutes; and enforcing the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 706-717 | ISSN:2251-6727

broad implementation of advanced technologies for wastewater treatment, such as AOPs, to guarantee efficient contaminant elimination at the source.

References

[1] Meyer MF, Powers SM, Hampton SE. An Evidence Synthesis of Pharmaceuticals and Personal Care Products (PPCPs) in the Environment: Imbalances among Compounds, Sewage Treatment Techniques, and Ecosystem Types. Environ Sci Technol 2019;53:12961–73.

[2] Arruda V, Simões M, Gomes IB. Synthetic musk fragrances in water systems and their impact on microbial communities. Water (Basel) 2022;14:692.

[3] Li J, Lu Y, Chen H, Zheng D, Yang Q, Campos LC. Synthetic musks in the natural environment: Sources, occurrence, concentration, and fate-A review of recent developments (2010-2023). Sci Total Environ 2024;922:171344.

[4] Borgå K. Ecotoxicology: Bioaccumulation. Reference Module in Earth Systems and Environmental Sciences, Elsevier; 2013.

[5] Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30:293–342.

[6] Salvito D. Synthetic musk compounds and effects on human health? Environ Health Perspect 2005;113:A802–3; author reply A803–4.

[7] Yang J-J, Metcalfe CD. Fate of synthetic musks in a domestic wastewater treatment plant and in an agricultural field amended with biosolids. Sci Total Environ 2006;363:149–65.

[8] Cavazzoli S, Scopetani C, Chelazzi D, Martellini T, Cincinelli A, Carretti E, et al. Effectiveness of conventional municipal wastewater treatment plants in microplastics removal: Insights from multiple analytical techniques. J Environ Sci (China) 2026;160:424–38.

[9] Jamil Emon F, Rohani MF, Sumaiya N, Tuj Jannat MF, Akter Y, Shahjahan M, et al. Bioaccumulation and Bioremediation of Heavy Metals in Fishes-A Review. Toxics 2023;11. https://doi.org/10.3390/toxics11060510.

[10] Barbieri MV, González MP, Araya Piqué V, Blasco J, Eljarrat E. Contaminants in fish and seafood from the marine environment: A global overview of current status and future perspective. Mar Pollut Bull 2025;219:118319.

[11] Fair PA, White ND, Wolf B, Arnott SA, Kannan K, Karthikraj R, et al. Persistent organic pollutants in fish from Charleston Harbor and tributaries, South Carolina, United States: A risk assessment. Environ Res 2018;167:598–613.

[12] Li W-L, Shunthirasingham C, Wong F, Smyth SA, Pajda A, Alexandrou N, et al. Assessing Contributions of Synthetic Musk Compounds from Wastewater Treatment Plants to Atmospheric and Aquatic Environments. Environ Sci Technol 2024;58:5524–33.

[13] Lee I-S, Kim U-J, Oh J-E, Choi M, Hwang D-W. Comprehensive monitoring of synthetic musk compounds from freshwater to coastal environments in Korea: with consideration of ecological concerns and bioaccumulation. Sci Total Environ 2014;470-471:1502–8.

[14] Su Y, Li F, Xiao X, Li H, Wang D, You J. Ecological risk of galaxolide and its transformation product galaxolidone: evidence from the literature and a case study in Guangzhou waterways. Environ Sci Process Impacts 2023;25:1337–46.

[15] Fang H, Li G, Yao S, Liang X, An T. Kinetic and mechanism studies of musk tonalide reacted with hydroxyl radical and the risk assessment of degradation products. Catal Today 2017;281:642–8.

[16] Schmeiser HH, Gminski R, Mersch-Sundermann V. Evaluation of health risks caused by musk ketone. Int J Hyg Environ Health 2001;203:293–9.

[17] Yamauchi R, Ishibashi H, Hirano M, Mori T, Kim J-W, Arizono K. Effects of synthetic polycyclic musks on estrogen receptor, vitellogenin, pregnane X receptor, and cytochrome P450 3A gene expression in the livers of male medaka (Oryzias latipes). Aquat Toxicol 2008;90:261–8.

[18] Lalik A, Szreder J, Grymel M, Żabczyński S,

Bajkacz S, Pielok M, et al. Estrogens and Progestogens in Environmental Waters: Analytical Chemistry and Biosensing Perspectives on Methods, Challenges, and Trends. Anal Chem 2025;97:8654–83.

[19] Liu X, Lu X, Hong J, Zhang J, Lin J, Jiang M, et al. Effects of long-term exposure to TDCPP in zebrafish (Danio rerio) - Alternations of hormone balance and gene transcriptions along hypothalamus-pituitary axes. Animal Model Exp Med 2022;5:239–47.

[20] Nash JP, Kime DE, Van der Ven LTM, Wester PW, Brion F, Maack G, et al. Long-term exposure to environmental concentrations of the pharmaceutical ethynylestradiol causes reproductive failure in fish. Environ Health Perspect 2004;112:1725–33.

[21] Luccio-Camelo DC, Prins GS. Disruption of androgen receptor signaling in males by environmental chemicals. J Steroid Biochem Mol Biol 2011;127:74–82.

[22] Burris-Hiday SD, Scott EE. Steroidogenic cytochrome P450 17A1 structure and function. Mol Cell Endocrinol 2021;528:111261.

[23] Goldstone JV, Sundaramoorthy M, Zhao B, Waterman MR, Stegeman JJ, Lamb DC. Genetic and structural analyses of cytochrome P450 hydroxylases in sex hormone biosynthesis: Sequential origin and subsequent coevolution. Mol Phylogenet Evol 2016;94:676–87.

[24] Odermatt A, Strajhar P, Engeli RT. Disruption of steroidogenesis: Cell models for mechanistic investigations and as screening tools. J Steroid Biochem Mol Biol 2016;158:9–21.

[25] Miyata K, Ose K. Thyroid Hormone-disrupting Effects and the Amphibian Metamorphosis Assay. J Toxicol Pathol 2012;25:1–9.

[26] Sabatino L, Vassalle C, Del Seppia C, Iervasi G. Deiodinases and the Three Types of Thyroid Hormone Deiodination Reactions. Endocrinol Metab (Seoul) 2021;36:952–64.

[27] Shan Z, Li S, Yu C, Bai S, Zhang J, Tang Y, et al. Embryonic and skeletal development of the albino African clawed frog (Xenopus laevis). J Anat 2023;242:1051–66.

[28] Tanizaki Y, Shibata Y, Zhang H, Shi Y-B. Analysis of Thyroid Hormone Receptor α-Knockout Tadpoles Reveals That the Activation of Cell Cycle Program Is Involved in Thyroid Hormone-Induced Larval Epithelial Cell Death and Adult Intestinal Stem Cell Development During Metamorphosis. Thyroid 2021;31:128–42.

[29] Hosseini E, Shahhoseini M, Afsharian P, Karimian L, Ashrafi M, Mehraein F, et al. Role of epigenetic modifications in the aberrant gene expression in polycystic ovary syndrome. Arch Med Sci 2019;15:887–95.

[30] Friesenhengst A, Pribitzer-Winner T, Miedl H, Pröstling K, Schreiber M. Elevated Aromatase (CYP19A1) Expression Is Associated with a Poor Survival of Patients with Estrogen Receptor Positive Breast Cancer. Horm Cancer 2018;9:128–38.

[31] Gong P, Madak-Erdogan Z, Li J, Cheng J, Greenlief CM, Helferich W, et al. Transcriptomic analysis identifies gene networks regulated by estrogen receptor α (ERα) and ERβ that control distinct effects of different botanical estrogens. Nucl Recept Signal 2014;12:e001.

[32] Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. Metabolism 2021;114:154338.

[33] Deichmann U. Epigenetics: The origins and evolution of a fashionable topic. Dev Biol 2016;416:249–54.

[34] Galan C, Krykbaeva M, Rando OJ. Early life lessons: The lasting effects of germline epigenetic information on organismal development. Mol Metab 2020;38:100924.

[35] Champagne FA. Epigenetic mechanisms and the transgenerational effects of maternal care. Front Neuroendocrinol 2008;29:386–97.

[36] Okuthe GE, Dube E, Mafunda PS. Effects of Pharmaceuticals and Endocrine-Disrupting Chemicals on Reproductive Biology of Aquatic Fauna: Penguins as Sentinel Species. J Xenobiot 2025;15. https://doi.org/10.3390/jox15040110.

[37] Metcalfe CD. Toxic effects of fragrances to aquatic organisms. The Handbook of Environmental Chemistry, Cham: Springer International Publishing; 2023, p. 37–46.

[38] Wang J, Wu F, Wang X, Ai S, Xi J, Liu Z, et al. From microbiota to metabolism: Unveiling the hidden ecological threat of galaxolide (HHCB) to zebrafish through aquatic microcosm. Environ Int 2025;202:109683.

[39] Yokokawa R, Watanabe K, Kanda S, Nishino Y, Yasumasu S, Sano K. Egg envelope formation of medaka Oryzias latipes requires ZP proteins originating from both the liver and ovary. J Biol Chem 2023;299:104600.

[40] Chen C, He W, Ni Z, Zhang X, Cui Y, Song X, et al. Bioaccumulation, trophic transfer and risk assessment of polycyclic musk in marine food webs of the Bohai Sea. Mar Pollut Bull 2024;202:116353.

[41] Li W, Wang S, Li J, Wang X, Fan B, Gao X, et al. Development of aquatic life criteria for tonalide (AHTN) and the ecological risk assessment. Ecotoxicol Environ Saf 2020;189:109960.

[42] Yazawa T, Imamichi Y, Uwada J, Sekiguchi T, Mikami D, Kitano T, et al. Evaluation of 17β-hydroxysteroid dehydrogenase activity using androgen receptor-mediated transactivation. J Steroid Biochem Mol Biol 2020;196:105493.

[43] Di Nardo G, Zhang C, Marcelli AG, Gilardi G. Molecular and Structural Evolution of Cytochrome P450 Aromatase. Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms22020631.

[44] Ortuño-Sahagún D, Pallàs M, Rojas-Mayorquín AE. Oxidative stress in aging: advances in proteomic approaches. Oxid Med Cell Longev 2014;2014:573208.

[45] Wang T, Zou H, Li D, Gao J, Bu Q, Wang Z. Global distribution and ecological risk assessment of synthetic musks in the environment. Environ Pollut 2023;331:121893.

[46] Castro-Alves V, Nguyen AH, Barbosa JMG, Orešič M, Hyötyläinen T. Liquid and gas-chromatography-mass spectrometry methods for exposome analysis. J Chromatogr A 2025;1744:465728.

[47] Aspromonte J, Lancioni C, Purcaro G. Solid-Phase Microextraction-Gas Chromatography Analytical Strategies for Pesticide Analysis. Methods Protoc 2022;5. https://doi.org/10.3390/mps5050082.

[48] Aceña J, Stampachiacchiere S, Pérez S, Barceló D. Advances in liquid chromatography-high-resolution mass spectrometry for quantitative and qualitative environmental analysis. Anal Bioanal Chem 2015;407:6289–99.

[49] Gomes G, Argolo ADS, Felix L da C, Bila DM. Interferences in the yeast estrogen screen (YES) assay for evaluation of estrogenicity in environmental samples, chemical mixtures, and individual substances. Toxicol In Vitro 2023;88:105551.

[50] Wielogórska E, Elliott CT, Danaher M, Connolly L. Endocrine disruptor activity of multiple environmental food chain contaminants. Toxicol In Vitro 2015;29:211–20.

[51] Vilar S, Costanzi S. Predicting the biological activities through QSAR analysis and docking-based scoring. Methods Mol Biol 2012;914:271–84.

[52] Low YS, Sedykh AY, Rusyn I, Tropsha A. Integrative approaches for predicting in vivo effects of chemicals from their structural descriptors and the results of short-term biological assays. Curr Top Med Chem 2014;14:1356–64.

[53] Tasselli S, Rogora M, Orrù A, Guzzella L. Behaviour of synthetic musk fragrances in freshwaters: occurrence, relations with environmental parameters, and preliminary risk assessment. Environ Sci Pollut Res Int 2023;30:109643–58.

[54] Hodkovicova N, Enevova V, Cahova J, Blahova J, Siroka Z, Plhalova L, et al. Could the musk compound tonalide affect physiological functions and act as an endocrine disruptor in rainbow trout? Physiol Res 2020;69:S595–606.

[55] Parolini M, Magni S, Traversi I, Villa S, Finizio A, Binelli A. Environmentally relevant concentrations of galaxolide (HHCB) and tonalide (AHTN) induced oxidative and genetic damage in

Dreissena polymorpha. J Hazard Mater 2015;285:1–10.

[56] Nishmitha PS, Akhilghosh KA, Aiswriya VP, Ramesh A, Muthuchamy M, Muthukumar A. Understanding emerging contaminants in water and wastewater: A comprehensive review on detection, impacts, and solutions. J Hazard Mater Adv 2025;18:100755.

[57] Matysiak J, Gorzel M, Skrzypek A. Synthetic musk odorants in cosmetic products. Arch Physiother Glob Res 2021;25:43–51.

[58] Oturan MA, Aaron J-J. Advanced oxidation processes in water/wastewater treatment: Principles and applications. A review. Crit Rev Environ Sci Technol 2014;44:2577–641.

[59] Pramanik R, Bodawar N, Brahme A, Kamble S, Dharne M. Comparative evaluation of advanced oxidation processes (AOPs) for reducing SARS-CoV-2 viral load from campus sewage water. J Environ Chem Eng 2023;11:109673.

[60] Silva JA. Advanced oxidation process in the sustainable treatment of refractory wastewater: A systematic literature review. Sustainability 2025;17:3439.

[61] Cronin MTD, Enoch SJ, Madden JC, Rathman JF, Richarz A-N, Yang C. A review of in silico toxicology approaches to support the safety assessment of cosmetics-related materials. Comput Toxicol 2022;21:100213.

[62] Priyadarshini E, Parambil AM, Rajamani P, Ponnusamy VK, Chen Y-H. Exposure, toxicological mechanism of endocrine disrupting compounds and future direction of identification using nano-architectonics. Environ Res 2023;225:115577.

[63] Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol 2017;18:83.

[64] Sanches PHG, de Melo NC, Porcari AM, de Carvalho LM. Integrating Molecular Perspectives: Strategies for Comprehensive Multi-Omics Integrative Data Analysis and Machine Learning Applications in Transcriptomics, Proteomics, and Metabolomics. Biology (Basel) 2024;13. https://doi.org/10.3390/biology13110848.

[65] Worku AK, Ayele DW, Teshager MA, Omar M, Yerkrang PP, Elgaddafi R, et al. Recent advances in wastewater treatment technologies: Innovations and new insights. Energy Reviews 2025:100164.

[66] Rafieenia R, Sulonen M, Mahmoud M, El-Gohary F, Rossa CA. Integration of microbial electrochemical systems and photocatalysis for sustainable treatment of organic recalcitrant wastewaters: Main mechanisms, recent advances, and present prospects. Sci Total Environ 2022;824:153923.

[67] Forbes VE, Calow P, Grimm V, Hayashi TI, Jager T, Katholm A, et al. Adding value to ecological risk assessment with population modeling. Hum Ecol Risk Assess 2011;17:287–99.