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Bioaccumulation and Ecotoxicity of Synthetic Musks in the Aquatic Environment

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Abstract Due to the fact that both nitro and polycyclic musk fragrances and their metabolites are not readily biodegradable in most sewage treatment plants and thus appear in the aquatic environment, the emphasis in this chapter is laid on understanding and evaluating their potential for bioaccumulation and hence their possible adverse impact (acute and chronic toxicity) on aquatic ecosystems. The bioaccumulation of these fragrances in aquatic organisms is principally governed by their inherent structure (parent compounds as well metabolites produced by microbial degradation in sewage treatment plants) and hence by their bioavailability, lipophilicity and the species specific capability of aquatic organisms to metabolize these compounds to readily excretable forms. Consequently, all potential adverse effects, whether acute, subchronic or chronic must be seen primarily as the result of the latter compound specific characteristics. Generally speaking nitro musk fragrances, due to their high bioaccumulation potential and higher resilience toward metabolic conversion appear to have potentially a greater environmental influence than their polycyclic counterparts. However, all presently available data, although primarily based on mammalian studies and limited aquatic toxicological assessments and despite their restriction in breadth and depth of detailed mechanistic understanding, suggest that neither of the musk fragrance classes pose an immediate or long-term hazard to the aquatic ecosystem despite their presence in environmental samples. However, prudence dictates that their accumulation in various organisms of several trophic levels in the aquatic ecosystems is unacceptable and that this situation should be ameliorated.

Keywords Nitro musks · Polycyclic musks · Bioaccumulation · Bioconcentration factors · Aquatic toxicity · Toxicity mechanisms

1 Introduction

In view of the yearly global production of nitro and polycyclic musk fragrances, estimated at approximately 2000 and 5600 tons, respectively (for the year 1996) [1–3], and the use of musks as fragrances and fragrance fixatives in a wide array of personal care products (e.g., washing detergents, detergents in general, perfumes, lotions, soaps and shampoos, cosmetics, etc.) it follows that most of these compounds will appear in municipal sewage treatment plants (STP). The removal of nitro musks (NMs) and polycyclic musks (PCMs) during municipal sewage treatment processes has been estimated at approximately 60–80% and 40–60%, respectively. The higher retention of NMs in the STP are explained by the presence of the aromatic ring and thus higher affinity for particles, a rather low water solubility due to the limited ring substitution with polar groups, and a moderately high lipophilicity (Table 1). In contrast, PCMs have a high water solubility, despite their inherently high lipophilicity (Table 1) and biological stability [4]. In view of the lipophilicity of NMs and PCMs and their broad form of application, it is not surprising to find these compounds as contaminants in the aquatic environment. Indeed, the concentrations detected in environmental samples range from ng L^{-1} to µg L^{-1} in effluent and surface waters [5]. The fact that NMs and PCMs can also be detected from µg kg^{-1} to mg kg^{-1} lipid weight in aquatic organisms [3, 6–9] raised serious concern as to their potential adverse effects on the aquatic ecosystem. Moreover, most recent analyses point to NM and PCM metabolites as being of greater environmental concern, due to greater metabolic stability and environmental persistence and consequently higher concentrations present in biological samples, e.g., in fish muscle, than the respective parent compounds [10–13].

The presence of not readily biodegradable compounds, i.e., musk fragrances in the aquatic environment raised major concerns, primarily in Europe, where the

Table 1 Common/tradename, abbreviation, CAS number and octanol-water partition coefficient (P_{OW}) for the most commonly used musk fragrances and their metabolites

Common/trade name	Abbreviation	CAS No.	P_{OW}	Reference
Musk xylene	MX	81-15-2	4.9	[2, 17]
2,4-di-aminomusk xylene	2,4-di-NH_2-MX	–	2.7–3.0	[25]
4-Amino musk xylene	4-NH_2-MX	107342-55-2	3.6–4.3	[2, 25]
2-Amino musk xylene	2-NH_2-MX	107342-67-6	2.7–4.3	[2, 25]
Musk ketone	MK	81-14-1	4.2–4.3	[2, 17]
2-Amino musk ketone	2-NH_2-MK	–	–	
Musk moskene	MM	116-66-5	4.4	[27]
Galaxolide	HHCB	1222-05-5	5.9–6.26	[13]
Tonalide	AHTN	1506-02-1; 21145-7-7	5.7–6.35	[13]
Celestolide	ADBI	13171-00-1	5.4	[3]
Phantolide	AHDI	15323-35-0	5.8	[3]
Cashmeran	DPMI	33704-61-9	4.5	[3]
Traseolide	ATII	68140-48-7	–	
Versalide	ATTN	88-29-9	–	

horrendous impact of polychlorinated biphenyls (PCBs), especially on fish otter (*Luttra luttra*) populations, is vivid in the memories of scientists, health officials, and the public. However, moderate to high lipophilicity, slow biodegradation, and the presence in water, sediments and edible fish tissues does not automatically warrant the comparison of musk fragrances with PCBs. Indeed, in order to assume adverse effects of any given compound in the environment, some information about its toxicity must be available. In most cases ecotoxicological data, although mostly restricted to acute standardized tests, is available and allows a rough judgment of potentially imminent acute adverse environmental effects. In those cases where no data to the acute or chronic environmental toxicity is at hand, a tentative risk assessment can be based on available mammalian toxicological data. In the case of musk fragrances, for which only a very limited number of ecotoxicological data are presently published, the broad mammalian toxicological dataset allows for an impression as to how environmentally dangerous these compounds potentially could or could not be [14, 15].

2 Bioaccumulation

All available analytical data, while showing the capability of musk fragrances to bioconcentrate in various aquatic species, do not demonstrate any capacity of these compounds for biomagnification in the aquatic ecosystem. Despite the fact that especially the nitro musk fragrance parent compounds demonstrate a moderate to high lipophilicity and potential for bioaccumulation/bioconcentration (Table 2), the capacity for bioconcentration/bioaccumulation must be differentiated in that for these compounds this appears more likely to be a function of momentary exposure of the species in question, rather than that of a lifetime upconcentration from a chronically contaminated environment. Indeed, age class analyses of fish taken from the Elbe river demonstrated no significant differences in tissue levels of NMs and PCMs from younger and older fish of the same species [16]. The concentrations of musk fragrances in the aquatic environment, including species, e.g., fish, are highly related to the distance from the STP [13]. In consequence and contrary to the situation with PCBs, the potential for toxicological effects resulting from musk parent compound exposure stems largely from the actual concentrations the species are exposed to via the ambient water in situ [17]. On the other hand, most recent analyses point to NM and PCM metabolites as being of greater environmental concern, due to greater metabolic stability and environmental persistence and thus higher concentrations present in biological samples, e.g., in fish muscle, than the respective parent compounds [2, 3, 10–12, 18–20]. In addition, primary degradation of PCM to more polar metabolites may lead to a different sorptive behavior and possibly to a higher bioavailability than the parent compounds [13, 21, 22]. However, despite the latter findings, which clearly highlight the necessity of additional clarifying experiments, there is a paucity of literature data with respect to the bioaccumulation and kinetics of musk metabolites in aquatic species. Indeed, such data would allow a better assessment of the risks posed by these metabolites for aquatic species, especially when considering the potential subacute-subchronic/chronic

Table 2 Bioconcentration factors (BCF_W) and bioaccumulation factors (BAF_W) (both based on a wet weight basis) of musk fragrances in various aquatic species

Abb.	Species (Latin name)	Species (common name)	BCF_W	BAF_W	Reference
MX	*Scardinus erythrophthalmus*	Rudd		290	[17, 18, 27,
	Tinca tinca	Tench		2400	28, 48–51]
	Carassius carassius/C. auratus	Crucian carp		7500	
	Anguilla anguilla	Eel		40,000	
	Dreissena polymorpha	Zebra mussel		1800	
	Cyprinus carpio	Common carp	640–6740		
	Oncorhynchus mykiss	Rainbow trout	1600, 4400	10–60	
	Lepomis macrochirus	Bluegill sunfish	1600–1700		
	–	Fish unspecified	1300		
	Xenopus laevis	S.A. Clawed frog	5030		
MK	*S. erythrophthalmus*	Rudd		60	[17, 18, 27,
	T. tinca	Tench		230	28, 49]
	C. carassius/C. auratus	Crucian carp		570	
	A. anguilla	Eel		1300	
	Dreissena polymorpha	Zebra mussel		390	
	Lepomis macrochirus	Bluegill sunfish	1380		
	Danio rerio	Zebrafish	455		
	–	Fish unspecified	2143		
	–	Fish unspecified	1100		
Musk Moskene	–	Fish unspecified	1300		[27, 28]
	X. laevis	S.A. Clawed frog	5830		
HHCB	*S. erythrophthalmus*	Rudd		20	[13, 18, 52]
	T. tinca	Tench		510	
	C. carassius	Crucian carp		580	
	A. anguilla	Eel	862 (BCF_I 3504)	290	
	Dreissena polymorpha	Zebra mussel		620	
	L. macrochirus	Bluegill sunfish	1584		
	D. rerio	Zebrafish	620		
AHTN	*S. erythrophtalmus*	Rudd		40	[13, 18, 52]
	T. tinca	Tench		280	
	C. carassius	Crucian carp		670	
	A. anguilla	Eel	1069 (BCF_I 5017)	400	
	Dreissena polymorpha	Zebra mussel		570	
	L. macrochirus	Bluegill sunfish	597		
	D. rerio	Zebrafish	600		

effects, e.g., endocrine modulation in fish and amphibians as discussed below or potential immuno-modulatory effects which have yet to be investigated.

3 Toxicity

The following paragraphs represent primarily a compilation of data for the acute, subacute, and potential for subacute-subchronic/chronic toxicity of musk fragrances and their metabolites in target species (algae, daphnia, fish, and amphibians).

3.1 Acute Toxicity

The acute toxicity and potential environmental effects of NMs and PCMs were summarized in several publications either using the EU-Technical Guidance Documents as a basis for environmental risk assessment [4, 13, 23, 24], test procedures in conformity with OECD guideline 201 and 202 for testing of chemicals [25–27], or test procedures identical or analogous to ASTM guideline E 1439-91 [28]. These publications include studies with algae (*Pseudokirchneriella subcapitata*), *Daphnia magna*, bluegill sunfish (*Lepomis macrochirus*), rainbow trout (*Oncorhynchus mykiss*), zebra fish (*Danio rerio*), fathead minnow (*Pimephales promelas*), and the South African clawed frog (*Xenopus laevis*). The most prominent results are compiled in Table 3.

The main focus of the latter studies was on musk xylene (MX), musk ketone (MK) and the three polycyclic musks AHTN (7-acetyl-1,1,3,4,4,6-hexamethyltetraline), HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-(*g*)-2-benzopyran) and ADBI (4-acetyl-1,1-dimethyl-6-*tert*-butylindane). Additional data can be found for the three amino metabolites of MX and MK [29] as well as for musk moskene, tibetene, and ambrette [27]. Toxicity of either NMs or PCMs was observed at rather high concentrations of these respective compounds, i.e., in many cases at or exceeding the inherent water solubilities (Table 3).

The mechanism(s) involved in the acute toxicity of the NMs and PCMs is presently unknown. However, a generalized narcosis, as previously demonstrated for various other organic compounds in fish and amphibians [30], may be suggested in view of the high concentrations necessary to induce acute mortality [14, 26–28] and the erratic behavior noted with daphnia [26, 27]. The latter findings are contrasted by the report of Behechti et al. [25] who found acute toxicity of low concentrations of the amino metabolites of MX, especially of the 4-amino-MX in *D. magna* (EC_{50}=250 ng L^{-1}; 95% confidence interval 230–280 ng L^{-1}). A subsequent re-investigation of the findings of Behechti et al. [25] by Giddings et al. [26] demonstrated an EC_{50-48h}=490 µg L^{-1} (95% confidence interval 400–600 µg L^{-1}) and therefore that the previous findings by Behechti et al. overestimated the toxicity of 4-amino-MX by approximately a factor 2000, most likely as the result from highly toxic impurities present in their stock solutions. The acute toxic concentrations of 4-amino-MX for *Daphina magna* thus are also approximately four orders of magnitude greater than those concentrations found in surface waters

Table 3 Compilation of acute and subacute toxicity data obtained with nitro and polycyclic musks invarious species, modified from Dietrich and Chou [14]. All data in mg L^{-1}

Species	Endpoint	MX	2-NH_2-MX	4-NH_2-MX	2,4-di-NH_2-MX	MK	MM	AHTN	HHCB	ADBI	Ref.
Algae	$EC_{50\,growth}$	NE[a]				0.244	–	>0.797	>0.854	–	[4, 13, 23]
	$EC_{50\,biomass}$	NE[a]				0.118	–	0.468	0.723	–	
Daphnia magna	24 h EC_{50}	NE[a]	1.07	>0.93	23.3	NE[a]	NE[a]	–	–	–	[4, 13, 23, 25–27]
	48 h EC_{50}	>5,6		0.49							
	21 days LC_{50}	0.680				0.338–0.675	NE[a]	0.341	0.293	–	
Oncorhynchus mykiss	21 days $EC_{50\,repro.}$	–				0.169–0.338	NE[a]	0.244	0.282	–	[4, 23]
	96 h LC_{50}	>1000				–	–	–	–	–	
Lepomis macrochirus	21 days LC_{50}	–				>0.50	–	–	–	–	[4, 13, 23]
	96 h LC_{50}	1.20				–	–	–	–	–	
Danio rerio	21 days LC_{50}	–				–	–	0.314	0.452		[23, 28, 30, 48]
	14 days $LC_{50\text{-adult fish}}$	0.4				–	–	–	–	–	
	96 h $LC_{50\text{-embryo}}$	>0.4				>0.4	>0.4	>0.67	>0.67	>1.0	
	96 h $EC_{50\text{-embryo-hatching}}$	>0.4				>0.4	>0.4	>0.67	>0.67	>1.0	
	8 week $LOEC_{repro.}$					0.033					
Pimephales promelas	96 h $EC_{50\text{-embryo-teratogen}}$	>0.4				>0.4	>0.4	0.18	0.39	0.69	[13]
Xenopus laevis	96 h $EC_{50\text{-embryo-growth}}$	>0.4				>0.4	>0.4	>1.0	>1.0	>1.0	[28, 30]
	32 days $LC_{50\text{-embryo-adult}}$	–				–	–	0.100	>0.140	–	
	96 h $LC_{50\text{-embryo}}$	>0.4				>0.4	>0.4	>2.0	>2.0	>4.0	
	96 h $EC_{50\text{-embryo-teratogen}}$	>0.4				>0.4	>0.4	>4.0	>4.0	>4.0	
	96 h $EC_{50\text{-embryo-growth}}$	>0.4				>0.4	>0.4	>1.0	>2.0	>4.0	

[a] NE=no effect found at concentrations exceeding compound solubility in H_2O.

and treated sewage, demonstrating that nitro musks and their metabolites pose a negligible acute environmental hazard [26].

Indeed, the comparison of the NM and PCM concentrations found in environmental samples [2, 3, 10–12, 19, 31] with those concentrations inducing acute toxicity in various aquatic species, as discussed above, strongly suggests that NMs and PCMs do not pose an acute risk for the aquatic ecosystem. This conclusion is also supported by the instrumentalized risk assessment processes for NMs and PCMs using the EU-Technical Guidance Documents [4, 23, 24], which predict no effects of these musk fragrances in the aquatic environment.

3.1.1
Developmental Toxicity

In contrast to the more narcosis-like effects described above, more specific effects were reported when embryos of *X. laevis* and *D. rerio* are exposed to PCMs but not NMs [14]. Both *D. rerio* and *X. laevis* embryos presented with a significant increase in malformations [14]. Surprisingly, while all three PCMs (ADBI, AHTN, HHCB) induced malformations in zebra fish embryos, malformations were observed in ADBI treated *X. laevis* embryos only. While both species presented with ventro-dorsal curvature of the tail, the concentrations necessary to induce malformations in *D. rerio* were approximately one order of magnitude lower than those necessary to produce the same effects in the amphibian embryos. Of the PCMs tested, AHTN demonstrated the greatest degree of teratogenicity, with the steepest dose-response curve, while ADBI was teratogenic at high concentrations only. AHTN induced malformations appear to be specific for cyprinid embryos, as tail-loss was noted in *P. promelas* embryos exposed to 0.067 or 0.14 mg AHTN L^{-1}, while no malformations were observed in *X. laevis* embryos exposed to AHTN or HHCB [14] or in *P. promelas* exposed to HHCB [13]. Of the three PCMs tested in a semi-static embryotoxicity test with *X. laevis*, AHTN and HHCB demonstrated a significant and dose-dependent effect on growth at concentrations below those which were acutely toxic to the embryos. No effects on growth were observed in zebra fish embryos, as the doses necessary to induce a significant growth inhibition exceeded those inducing acute toxicity (Table 3). Similar effects were noted in *P. promelas* exposed to 0.140 mg HHCB l^{-1} but not for AHTN [13].

3.2
Subchronic/Chronic Toxicity

At present, only limited data are available for assessing the risk to the aquatic environment, i.e., the populations of aquatic species exposed subchronically or chronically to low concentrations of parent compounds and metabolites of NMs and PCMs. In general, there are three potential adverse interactions of xenobiotics with the health and sustainability of a population that are of primary importance: (i) an extremely high incidence of pathological changes, e.g., tumors [32] resulting from genotoxic or a tumor promoting activity; (ii) suppression of the immune system and thus higher susceptibility of the population to pathogens

[33]; and (iii) endocrine modulation affecting the reproductive success of the population.

Neither the parent compounds nor the metabolites of NMs and PCMs have been demonstrated to possess carcinogenic activity, with the exception of a species-specific promotion of liver tumors at high concentrations of MX observed in mice [34]. This process was shown to be not of genotoxic [35, 36], but rather of an epigenetic nature, i.e., driven by the induction of microsomal enzymes, particularly those of the CYP2B family [37], and the pattern of induction was consistent with that observed for phenobarbital, the classical CYP2B inducer and mouse liver carcinogen [38, 39].

No information is as yet available regarding the potential interaction of NMs and PCMs on immune parameters of aquatic species. However, the present expectation is that no immune-suppressive activity is to be expected in aquatic species as no evidence was found suggesting immune-suppressive activity of these compounds in mammalian species exposed subchronically or chronically to high concentrations of these compounds [34, 40, 41].

3.2.1 *Endocrine Modulation*

Although the present database on potential endocrine modulating activity of NMs and PCMs is still rather scant, the compilation of mammalian data and data from in vitro assays with cells and tissue homogenates from aquatic species suffices for a primary assessment, at least of the potential (anti)estrogenic activity of these compounds. Neither subchronic or chronic administration of NMs, PCMs, or mixtures of NMs and PCMs [34, 40, 41] suggests any form of (anti)estrogenic activity in rodent species. The basis for this assessment was organ weight and histopathological examination of the uterus, seminal vesicles, mammary gland, testes, ovaries, and vaginas. These findings are corroborated by a study of Seinen et al. [42] who exposed juvenile mice to high dietary levels of AHTN and HHCB and found no evidence for an increase in uterine weight. On the other hand, the same scientists reported a very weak estrogenic activity of both compounds using ERα- and ERβ-dependent gene transcription assays with human embryonal kidney 293 cells. The reported estrogenic activity was approximately six to eight orders of magnitude lower than the endogenous ligand estradiol (E_2). The latter findings demonstrated that only extremely high concentrations of AHTN and HHCB have measurable estrogenic potency and that the current levels of wildlife and human exposure to these compounds are too low to induce any estrogenic effects in the exposed species. The interaction of the PCMs with the hepatic estrogen receptor(s) of rainbow trout, carp, or the amphibian *X. laevis* was also shown in an in vitro competitive binding assay [14]. In comparison to the endogenous ligand E_2, approximately four orders of magnitude higher concentrations of AHTN were necessary to elicit the same degree of ligand competition (IC_{50}) in the *X. laevis* receptor binding assay. Very weak binding of AHTN and HHCB were found in the rainbow trout receptor binding [14], corroborating the findings by Seinen et al. [42]. Neither AHTN nor HHCB, but ADBI bound to the carp estrogen receptor [14], corroborating earlier findings by Smeets et al.

[43], who investigated AHTN and HHCB induced synthesis of vitellogenin in carp hepatocytes in vitro. Neither of the two compounds was capable of inducing vitellogenin in this system, suggesting that these compounds do not interact with the fish estrogen receptor(s) to the degree or with the high concentrations necessary for estrogen dependent gene transcription. Although metabolites of AHTN and HHCB, as found in environmental samples [3, 10, 12], were not analyzed for (anti)estrogenic activity, it can safely be assumed that these metabolites were also formed during incubation of the primary carp hepatocytes used as the screening method for estrogenic activity. If indeed these metabolites had any form of estrogenic activity the lack of vitellogenin induction in the carp hepatocyte system suggests that the metabolites were not formed in adequate concentrations to have an estrogenic effect. Overall it can be concluded that the current environmental PCM levels are too low to induce estrogenic effects in aquatic species.

In contrast to the PCMs neither of the two nitro musk parent compounds (MX and MK) had any competitive binding activity to either the rainbow trout or the Xenopus estrogen receptor(s). However, amino metabolites of MX and MK, formed during the sewage treatment process, were able to bind to the estrogen receptors of rainbow trout and *X. laevis*. The concentrations of the 2-NH_2-MX metabolite necessary to displace 50% of the endogenous ligand at the rainbow trout estrogen receptor(s) was approximately six orders of magnitude greater than that of the endogenous ligand (E_2) itself, again demonstrating that unrealistically high concentrations of these metabolites were needed to elicit any estrogenic activity in rainbow trout. Surprisingly the binding curves derived from the *X. laevis* estrogen receptor binding assay, demonstrated that all three known amino metabolites of MX and MK were able to compete with the endogenous ligand. The concentrations necessary for competition were only two to three orders of magnitude higher than those of E_2. Furthermore, the concentrations of 2-NH_2-MX necessary for E_2 competition at the *X. laevis* estrogen receptor(s) were nearly three orders of magnitude lower than those needed for competing at the rainbow trout estrogen receptor(s). The latter suggests that there are some species-specific susceptibilities with regard to potential estrogenic activities of nitro musk metabolites. Indeed, the findings in the *X. laevis* system are unique in that these in vitro findings were indicative for the endocrine modulating effects observed for bisphenol A (BA) in vivo [44]. Chronic exposure of *X. laevis* embryos to low concentrations of BA induced a feminization of male embryos [45]. Although the above in vitro systems may be indicative that some of the NM metabolites and PCMs may have the potential for endocrine modulation in aquatic species, the mere interaction of a xenobiotic with the estrogen receptor(s) of a given aquatic species does not imply that this interaction will also lead to all of the specific associated downstream events. The latter observations stand in stark contrast to the findings presented by Carlsson et al. [46] who reported reduced gonado-somatic and hepato-somatic indices as well as dose-dependent reduced fecundity and fertility in female zebra fish fed for eight weeks with feed containing 10 mg MK g^{-1} dry weight (dw). It is interesting to note that while exposed female fish fed with 10 mg MK g^{-1} dw for eight weeks were reported to contain 587 µg MK g^{-1} wet weight in fish muscle, no simultaneous analysis of the exposure water was con-

ducted to demonstrate whether the high body concentration in the female fish actually resulted from the contaminated feed, or whether it was a mere reflection of the water concentrations of musk ketone resulting from decaying feed.

4 Conclusions

Although the present database for ecotoxicological effects of NMs and PCMs and of their respective metabolites is still too small for a concluding risk assessment, there is little evidence that would suggest that these compounds, despite their overt presence in environmental samples, generally would have an adverse impact on the aquatic ecosystem. The concentrations of musk fragrances in the aquatic environment are highly related to the distance to the STP [13]. Indeed, as indicated also via the comparison between the tissue levels of various ages of fish exposed to NMs and PCMs, no biomagnification within the same species (age classes) or various trophic levels appears to occur [16]. In consequence and contrary to the situation with PCBs, the potential for toxicological effects resulting from musk exposure stems largely from the actual concentrations the species are exposed to via the ambient water in situ [17] and this risk appears to be negligible when using the presently available database for risk estimation. However, as pointed out above, amphibians appear to be more susceptible to endocrine modulating compounds than most of the species investigated so far [45]. In light of this, the interaction of the MX and MK metabolites with the estrogen receptor of *X. laevis* [47] must be taken more seriously and should be encouragement to investigate the mechanisms of this interaction, the potential effects and risks associated with these amino metabolites for amphibians in more detail. Similarly, the fact that for the first time a laboratory study with zebra fish, although unconventional in its approach and lacking detail in many important aspects [46], has demonstrated a significant effect of high doses of musk ketone (or also its metabolite) on reproduction (fecundity and fertility), indicates that long-term effects should be investigated, especially including several generations of a given aquatic species, despite the overall environmentally unproblematic appearance of musk fragrances and their metabolites.

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