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Title: Prioritisation approach to score and rank synthetic musk compounds for environmental risk assessment

Short title: Prioritisation of synthetic musks

Authors: Vera Homem*, José Avelino Silva, Nuno Ratola, Lúcia Santos, Arminda Alves*

LEPABE – Laboratory for Process Engineering, Environment, Biotechnology and Energy, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal

*Correspondence to:

Vera Homem, LEPABE – Laboratory for Process Engineering, Environment, Biotechnology and Energy, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal, Tel.: +351 22 041 4947, e-mail address: vhomem@fe.up.pt

Arminda Alves, LEPABE – Laboratory for Process Engineering, Environment, Biotechnology and Energy, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal, Tel.: +351 22 508 1883, e-mail address: aalves@fe.up.pt

Abstract

BACKGROUND

Synthetic musks are massively used in personal care and cosmetic products and they reach the environment mainly due to the fact that they are not completely removed from wastewater treatment plants (WWTPs). In this work, an innovative and simple chemical scoring and ranking approach was developed as a screening tool to evaluate the overall impact of musks on the environment, identifying priority compounds. This system is idealised as an important tool for a subsequently feasible environmental risk assessment of musks that may represent the overall contamination on a regional scale.

RESULTS

Physicochemical and toxicological properties of 18 synthetic musks estimated by (Q)SAR were successfully used for the chemical scoring and combined with observed data to estimate the environmental impact posed by these compounds on four environmental compartments.

CONCLUSION

The prioritisation approach for musks shows that the risk of a compound can vary depending on the compartments, although HHCB posed a high to very high risk to all of them. For instance, AHMI has a relevant risk to soil and air, but very low to low in water and sediments, while AHTN was considered to be of medium risk for water and soil, but of a very high risk to sediments and air.

Keywords: Synthetic musks, prioritisation, environment

INTRODUCTION

Cosmetics, toiletry and fragrances represent nowadays a significant share of the nations' Gross Domestic Product, implying an increasing use of these personal care products. Among the great diversity of chemicals employed in their production, synthetic musks are used as fragrance additives and fixative compounds in several personal care and household products like perfumes, shampoos, detergents, etc. After consumption, about 77% are drained into the sewer system[1, 2], reaching the wastewater treatment plants (WWTPs). Because of their chemical characteristics, such as partial biodegradability, they are not completely removed from WWTPs, accumulating either in sludge or in the effluents[3] and possibly contaminating natural waterways. As the input is currently significantly higher than the output, the net balance points to an accumulation over the years.

Despite their high production rates, concerns about synthetic musks have only recently emerged among the scientific community. Their common use as fragrance fixatives in scented products combined with their lipophilicity, persistence and potential biological effects, as well as the different trends of use in diverse communities, may be hazardous to ecosystems[4]. However, due to the lack of information, there are no certainties about the real impact of these compounds on the environment. Therefore, it is essential to develop expeditious protocols for the selection of specific musk compounds and matrices to be considered as priorities for future environmental risk assessment (ERA) studies.

The risks of exposure to synthetic musks have been estimated by environmental risk assessment (ERA) protocols, but only regarding individual compounds. For example, a complete and detailed ERA for galaxolide (HHCB), the most used musk, concluded in 2008 that there is no risk within all scenarios[5], but this assessment is still under discussion, as new data raised new concerns. Also, similar ERAs for the most recently produced musks are not found in literature. On the other hand, the number of synthetic musks has been increasing and exposure assessment studies have to cope with the difficulty of developing complex analytical methods to detect such a large number of chemicals at extremely low concentrations in diverse matrices (waters, sludge, air, sediments, soils, landfill leachates, animals or biota).

Several prioritisation and ranking schemes have been proposed in the literature[6-10]. Bu *et al.*[11] reviewed and evaluated 27 different screening systems to set the priority of chemical substances posing risk to human health. The majority of systems are hazard-based, in which the actual environmental concentrations are not selected as endpoints to characterise exposure due to the lack of data. The authors recommend a risk-based approach, although recognizing two critical issues: the characterisation of effect and exposure, where multiresidue analytical methods could overcome the problems with data scarcity.

Regarding personal care products, Gouin *et al.*[6] applied the RAIDAR model (Risk Identification and Ranking) to prioritise chemicals used in personal care products in India, although musks were not included. Chemicals such as triclosan, butylhydroxytoluene, benzophenone-3, among others, consistently showed high risk in all scenarios, but the authors admitted some limitations on the assumptions used when estimating emissions. Kumar and Xagoraraki[7] also presented a ranking system for pharmaceutical, personal care and endocrine-disrupting chemicals applied to US surface and drinking waters. Nitromusks were in the top-ten compounds scoring highest among 100 compounds, but different lists were obtained according to the type of matrices analysed. On the other hand, Ortiz de García *et al.*[8] used the (Q)SAR approach (Quantitative study of Structure-Activity Relationship) to establish a ranking of concern regarding 96 PPCPs. The authors reported that fragrances (musks), hormones and antidepressants, among others, have the highest levels of toxicity. However, the number of musks was limited to 6 in this study and therefore there is still an urgent need to prioritise risks within this family of chemicals.

For this purpose, an innovative and simple chemical scoring and ranking approach was developed as a screening tool to evaluate the overall impact of musks on the environment, setting expeditious protocols and matrices to be considered as priorities. This risk-based approach has been inspired in two previous studies: (i) PestScreen[12] for ranking pesticides by their environmental and toxicological concern and (ii) SCRAM (Chemical Scoring and Ranking Assessment Model), proposed by Snyder *et al.*[13], who developed it for the Great Lakes region of North America, but is not considered site-specific. Both rely on combining measures of chemical toxicity with occurrence and information on the overall environmental persistence, long-range transport potential and human population intake fractions.

The importance of this work relies on the identification of a limited number of synthetic musk compounds as "potentially relevant" for the different environmental compartments, therefore reducing the analytical efforts for further monitoring and developing more elaborated ERA studies.

EXPERIMENTAL

Prioritisation strategy and assumptions

Eighteen synthetic musks (5 nitromusks, 6 polycyclic, 5 macrocyclic and 2 alicyclic musks) were selected based on their detection in the environment (**Fig. 1**). Their ranking for each matrix (water, air, soil and sediments) was established according to physicochemical and toxicological properties.

Two main criteria (exposure potential and ecotoxicity) were defined and within each one, attributes and sub-attributes were evaluated (**Fig. 2**). The "exposure potential" was represented by two attributes: "bioaccumulation" and "environmental persistence", being the latter further divided into two sub-attributes, "chemical persistence" and "environmental mobility". Individual scores were assigned between 1 (very low impact) and 5 (very high impact).

For each compartment, bioaccumulation was evaluated by the bioconcentration factors (BCF). This parameter, defined as the ratio between the concentrations of a given chemical in the tissue of an organism and in the surrounding medium (considering that the exposure is exclusively due to the contact with the contaminated medium)[14], provides an indication of the potential for a chemical to accumulate in the lipid fraction (fatty tissue) of the organisms. In this case, four organisms were selected to represent each matrix: fish (water), earthworm (soil), plant (air) and benthic invertebrate (sediment). BCF in fish was estimated by the (Q)SAR modelling software EPI Suite.[15] According to the REACH Regulation N.º 1907/2006[16], a substance is considered very bioaccumulative if $BCF_{fish} > 5000$ L kg^{-1} and bioaccumulative if $BCF_{fish} > 2000$ L kg^{-1}. For this reason, these values were set for scores 5 and 4, respectively. The lowest scores were defined based on the SCRAM methodology[13].

The BCF in earthworms was modelled with the following equation[17]:

$$BCF_{earthworm} = \frac{0.84 + 0.012 \times K_{OW}}{RHO_{earthworm}} \qquad \text{(Eq. 1)}$$

where K_{OW} is the octanol-water partition coefficient and the RHO is the density of the earthworm (set at 1 kg L^{-1}). The criteria used to classify the bioaccumulation potential in earthworms (soil) are described in **Fig. 2**, i.e. compounds with values above 1000 L kg^{-1} are considered very bioaccumulative, while those with values below 1 L kg^{-1} are considered non-bioaccumulative[13, 18].

The major route for the plant uptake of semi-volatile hydrophobic compounds is the atmosphere. Therefore, the BCF in plants (only considering the contribution of air), was estimated by[19]:

$$BCF_{plants} = f_{air} + VWC \times K_{WA} + VLC \times K_{OA} \qquad \text{(Eq. 2)}$$

where f_{air} is the fraction of the plant (wet weight) in contact with the air (set as 19%), VWC is the plant's water content (assumed as 17%), K_{WA} is the water-air partition coefficient, VLC is the plant's lipid content (set as 5%) and K_{OA} is the octanol-air partition coefficient. K_{WA} was determined as follows:

$$K_{WA} = \frac{C_{water}}{C_{air}} = \frac{R \times T}{H_C} \qquad \text{(Eq. 3)}$$

where R is the ideal gas constant (8.205×10^{-5} atm m^3 mol^{-1} K^{-1}), T is the temperature (298 K) and H_C the Henry's law constant (atm m^3 mol^{-1}). H_C and K_{OA} were also estimated by the (Q)SAR modelling software EPI Suite.[15] Therefore, compounds with H_C values below 10^{-7} atm m^3 mol^{-1} and log K_{OA} above 8 (non-volatile) have the highest score ($BCF_{plants} > 5\,000\,000$), while those with H_C values above 10^{-1} atm m^3 mol^{-1} and log K_{OA} below 4 (very susceptible to volatilisation) have the lowest ones [20] ($BCF_{plants} \leq 500$).

The sediment-to-benthic invertebrate bioconcentration factors were determined assuming that moisture content of the organism is 83.3%[21]:

$$\log BCF_{benthicinvertebraes} = 0.819 \times \log K_{OW} - 1.146 \qquad \text{(Eq. 4)}$$

The K_{OW} was once again used to estimate the BCF $_{\text{benthic invertebrates}}$ parameter. Compounds with log $K_{OW} > 5$ (BCF > 1000) have an affinity towards the lipophilic tissues of the benthic invertebrate organisms, whereas those with log $K_{OW} < 2$ (BCF ≤ 3) have a greater tendency to accumulate in the sediment phase.

The chemical persistence was scored based on ranges of half-lives ($t_{1/2}$) in the four environmental compartments. The half-lives in air were estimated based on the reactions with the hydroxyl radicals and ozone, whereas in water, soil and sediment were calculated based on abiotic (degradation via oxidation, reduction or hydrolysis reactions without the participation of living organisms) and biodegradation processes. The scores for half-lives in water, soil and sediments were defined based on the REACH regulation[16] (Persistent: $t_{1/2\ \text{water}} > 40$ days, $t_{1/2\ \text{soil or sediment}} > 120$ days; Very persistent: $t_{1/2\ \text{water}} > 60$ days, $t_{1/2\ \text{soil or sediment}} > 180$ days). For air, it was considered that compounds with half-lives in the range of hours are short-lived in air (low score) and those present for longer than 40 days are considered extremely persistent.[20, 22, 23]

The environmental mobility was expressed by different physicochemical properties. The Henry's law constant (H_C), defined as the ratio of a chemical's concentration in the gas phase to its concentration in the aqueous phase at equilibrium, was used to determine the tendency of volatilisation from the water to the air. According to these criteria (**Fig. 2**), synthetic musks with H_C values above 10^{-5} atm m^3 mol^{-1} are susceptible to volatilisation, while those below 10^{-7} atm m^3 mol^{-1} are considered non-volatile, therefore remaining in the water compartment.[18]

The partitioning coefficient between the organic carbon fraction in soil or sediment and the system soil-water or sediment-water (K_{OC}) was used to express the potential for the chemical to be sorbed onto soil or sediment from the water compartment. Values of log $K_{OC} > 4.5$ indicate a very strong sorption and consequently, negligible migration to the aqueous phase. Conversely, values below 1.5 show a very low sorption capacity, but a rapid migration to the water compartment.[18]

The volatilisation potential from soil to air was assessed by the soil-air partitioning coefficient (K_{SA}), estimated by the following equation[24]:

$$K_{SA} = \frac{C_{soil}}{C_{air}} = \frac{C_{water}}{C_{air}}\left(\frac{1}{r}+k_d\right) = \frac{R \times T}{H_C}\left(\frac{1}{r}+k_d\right) \quad \text{(Eq. 5)}$$

where R is the ideal gas constant (8.205x10^{-5} atm m^3 mol^{-1} K^{-1}), T is the temperature (298 K), r is the weight of soil/weight of water ratio (for these calculations a ratio of 6 was used, corresponding to a soil moisture of approximately 17%), k_d is the distribution coefficient characterising the partitioning of a chemical between soil and soil-water and H_C us the Henry's law constant. The k_d parameter was derived from the chemical partitioning coefficient between the organic carbon in soil and the soil-water system (K_{OC}, L kg^{-1})[24]:

$$k_d = \frac{K_{OC}}{1.724} \times \frac{\%OC}{100} \quad \text{(Eq. 6)}$$

where %OC is the organic carbon content of the soil (considered 2.0%) and 1.724 is the conversion factor for soil organic carbon in soil organic matter.[25] The criteria used to categorise the volatilisation potential from soil to air of synthetic musks using the log K_{SA} are described in **Fig. 2**, i.e. pollutants with log $K_{SA} < 6$ have relatively low affinities for the soil phase and therefore, have a greater ability to volatilise (highest scores). In contrast, contaminants with log $K_{SA} > 8$ exhibited strong adsorption to soil and low volatilisation potential.[22]

The deposition potential was expressed by the fraction of the pollutants linked to airborne particles (Ø). This was calculated from the Mackay adsorption model[26]:

$$\phi = \frac{k_{pa} \times TSP}{1 + k_{pa} \times TSP} \quad \text{(Eq. 7)}$$

where k_{pa} is the particle-gas partition coefficient (m^3 µg^{-1}) and TSP is the total concentration of suspended particles (considered 80 µg m^{-3} in this case). The k_{pa} was estimated by Eq. 8 [27, 28]:

$$k_{pa} = \frac{k_{QA}}{10^9 \times \rho} \quad \text{(Eq. 8)}$$

where k_{QA} is the dimensionless aerosol-air partition coefficient (m$^3_{\text{air}}$ m$^{-3}_{\text{aerosol particles}}$), the factor 10^9 converts kilograms of aerosol into micrograms and ρ is the density of the aerosol, assumed as 2000 kg m^{-3}. The k_{QA} was calculated by[28]:

$$k_{QA} = \frac{6.00 \times 10^6}{P_l^S} \quad \text{(Eq. 9)}$$

where $P^S{}_l$ is the saturation liquid-phase vapour pressure of the compound (Pa) and the factor $6.00\text{x}10^6$ Pa is an estimate of the sorption of chemicals to urban aerosols, based on PAHs data.

Correlating Eq.8 and Eq.9 results in the following expression[29]:

$$k_{pa} = \frac{6.00\times10^{6}}{P_l^S\times10^{9}\times2000} = \frac{3.00\times10^{-6}}{P_l^S} \qquad \text{(Eq. 10)}$$

As can be seen in **Fig. 2**, if the fraction sorbed to airborne particles is more than 90%, the deposition is very high and, therefore, the probability of the synthetic musk to be found in air is very low. In contrast, if the fraction sorbed is lower than 10%, the compound has low deposition potential and may remain in the atmosphere.

The environmental persistence score was determined as the average score of the two sub-attributes (chemical persistence and environmental mobility). This score determines which path is taken to rank toxicological properties, i.e. if the contaminant has a persistence of 1 or 2 it is scored for acute toxicity[13]. On the other hand, if the environmental persistence is 3 to 5, the synthetic musks are scored for subchronic/chronic toxicity.

The acute toxicity was assessed through the median lethal concentration (LC_{50}) for fish (96-h), daphnia (48-h) and earthworm (14-day) or half maximal effective concentration (EC_{50}) for algae (96-h) (**Fig. 2**). In the aquatic compartment, three trophic levels were considered (fish, daphnia and algae) and the highest score obtained was selected as the chemical score for the acute aquatic toxicity category (worst-case scenario). The acute toxicity scores for soil and sediments were calculated in a similar way. However, for the soil and sediments only a trophic level was considered (earthworms and daphnia, respectively). When the environmental persistence indicates that the contaminant has a subchronic/chronic toxicity, scores were established likewise to those for acute toxicity, but based on the chronic toxicity value (ChV). This is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC), both estimated by the EPI Suite software.[15] If a chemical is not soluble enough to reach the effect concentrations mentioned above (water solubility is lower than an effect concentration), a score of 1 is assumed for the ecotoxicity. Toxicity in air was not evaluated due to lack of data on the subject.

The final composite score for each matrix was determined based on SCRAM[13]. The ecotoxicity score was added to the multiplication of the bioaccumulation and environment persistence scores weighted by a factor of 1.5 to increase the influence of these properties on the final score:

$$\text{Final Score}_{\text{water, soil and sediment}} = \text{Score}_{\text{Bio}} \times \text{Score}_{\text{Persist}} \times 1.5 + \text{Score}_{\text{Ecotox}} \qquad \text{(Eq. 11)}$$

$$\text{Final Score}_{\text{air}} = \text{Score}_{\text{Bio}} \times \text{Score}_{\text{Persist}} \times 1.5 \qquad \text{(Eq. 12)}$$

where *Bio* is the bioaccumulation, *Persist* the environmental persistence and *Ecotox* the ecotoxicology.

Final scores range from 3.0 to 43.0 for water, soil and sediment ($3.0 \leq \text{Score} \leq 5.0$, Very low; $5.0 < \text{Score} \leq 12.0$, Low; $12.0 < \text{Score} \leq 22.0$, Moderate; $22.0 < \text{Score} \leq 35.0$, High; $35.0 < \text{Score} \leq 43.0$, Very high) and from 1.0 to 25.0 for air ($1.0 \leq \text{Score} \leq 3.0$, Very low; $3.0 < \text{Score} \leq 7.0$, Low; $7.0 < \text{Score} \leq 13.0$, Moderate; $13.0 < \text{Score} \leq 19.0$, High; $19.0 < \text{Score} \leq 25.0$, Very high). Synthetic musks falling into the "Very high" and "High" ranges were considered to have the greatest impact on environment, being potentially dangerous.

Environmental risk

According to the World Health Organization (WHO), “risk is the probability of an adverse effect in an organism, system or (sub)population caused by exposure to an agent under specific circumstances” [30]. A compound can pose a risk only when two factors meet: first, the potential of the compound to cause harm and second, the presence of this compound in the same medium in which the organism or population live. While the above-described chemical scoring procedure accomplishes the first part, only the assessment of its presence in the studied compartment can shed light on an effective evaluation of a potential risk. Therefore, mathematically, the environmental risk of a compound can be calculated multiplying its final composite score and its detection frequency (used as a measure of the probability of exposure).

The frequency of occurrence can be obtained by two ways: a monitoring scheme or through previously published data. While the former offers the advantage of fully controllable parameters (e.g. selection of sampling points, type of samples, method of analysis, etc.) and full insight into the obtained dataset (e.g. individual concentrations of each sample, target analytes recovery rates and uncertainties etc.), it requires expensive field-based set-up, sampling and analysis, which often is not feasible. In literature, although the available information may be not as comprehensive as in a fit-for-purpose monitoring scheme, it may still be valuable for a risk assessment. Still, a careful definition of criteria (timeframe of sampling, geographical area, type of samples, etc.) is important in order to avoid biased inputs due to an incoherent dataset.

Meta-analysis of synthetic musks data in literature

A meta-analysis of the presence of musks in the four matrices in study (water, air, soil and sediments) was performed in order to assess the exposure to this kind of compounds, being the data obtained via a systematic bibliographic review of literature using several scientific databases (Scopus®, Elsevier®, Taylor & Francis®, ACS Publications®, Springer® and Google® Scholar). As consumption patterns and legislation vary geographically, this search was restricted to samples collected in Europe between 2000 and 2014. Whenever the information on the sampling date was missing, this was estimated to have occurred six to twelve months prior to manuscript submission. The frequency of detection, defined as the results above the limit of detection (LOD), were either retrieved directly from the publication or calculated from individual sample results. For water and sediment matrices, data regarding superficial freshwater (river and lakes) and respective sediments was considered. For air matrices, occurrences in outdoor samples were taken into account. For soils, data on natural and amended soils were collected.

Environmental risk

The environmental risk was calculated for each synthetic musk and each of the four environmental compartments as the final composite score times the detection frequency:

$$\text{Environmental risk} = \text{Final score} \times \text{Detection frequency (\%)} \qquad \text{(Eq. 13)}$$

Musks with no occurrence data available were not considered. The detection frequency ranged between 0 and 100%, but for the composite score the ranges were different. In water, soil and sediments, possible composite scores ranged from 3.0 to 43.0, which results in environmental risk scores of 0.0 to 43.0. Qualitatively, this environmental risk score can be sub-classified as follows: $0.0 < \text{Score} \leq 1.0$, Very low; $1.0 < \text{Score} \leq 4.8$, Low; $4.8 < \text{Score} \leq 13.2$, Moderate; $13.2 < \text{Score} \leq 28.0$, High; $28.0 < \text{Score} \leq 43.0$, Very high. For air, the final combined scored was between 1.0 and 25.0, and consequently the environmental risk score ranged between 0.0 and 25.0. Sub-classifications were: $0.0 < \text{Score} \leq 0.6$, Very low; $0.6 < \text{Score} \leq 2.8$, Low; $2.8 < \text{Score} \leq 7.8$, Moderate; $7.8 < \text{Score} \leq 15.2$, High; $15.2 < \text{Score} \leq 25.0$, Very high.

RESULTS AND DISCUSSION

Chemical prioritisation of synthetic musks

The main objective of the chemical prioritisation was to evaluate the impact of musks in the different environmental compartments through the analysis of the physicochemical and toxicological properties (**Tables 1 to 4**). In water and soil matrices, most of the contaminants studied exhibited a low impact. This situation was expected for water, due to the generally low solubility of synthetic musks. However, some exceptions are HHCB and musk muscone, with a high impact (score of 23.0) on water, and most polycyclic musks (ADBI, AHMI, ATII, HHCB, AHTN), nitromusks (MX, MM, MK and MT) and musk muscone with a strong impact on soil (scores between 24.0 and 31.0). In air, ADBI, AHMI, ATII, MA, MT and helvetolide showed a very high impact (score of 20.0). This was mainly due to the high volatility of these compounds coupled with their low deposition potential. ATII, HHCB, AHTN, ADBI, AHMI, MT, MM and musk muscone had a very high impact (scores of 42.0 and 43.0) on sediments (low solubility of the contaminants).

Occurrence of synthetic musks – Data in literature

The incidence of synthetic musks in aqueous matrices is quite well documented, by the 15 articles comprising 669 samples, found and compiled in **Table S1 (Supporting Information)**. In one study, Ramírez et al.[31], no information about the number of samples was given. However, the frequency of detection was indicated and therefore this publication was also taken into account. In water matrices, the most frequently detected (and at the same time the most studied) musks, are HHCB and AHTN, with presences of 85% in 669 samples and 83% in 481 samples, respectively. These two musks also showed the highest levels, up to 2184 ng L^{-1} for HHCB and to 550 ng L^{-1} for AHTN. This is in agreement with the fact that both compounds are the most used musks, accounting for 95% of the EU market[32]. DPMI was also often found (in approximately half of the samples) and at levels reaching 1377 ng L^{-1}. While the nitromusks banned by the EU (MA, MM and MT) were not detected in all samples, this is not the case for the restricted ones. In fact, MX was detected in 24% of 74 samples and MK in 20% of 75 samples. Exaltolide and romandolide were the only macrocyclic and alicyclic musks detected, with respective frequencies of 12% and 7% in 42 samples. This may be due to their inherently better biodegradability[33], or to the fact of being novel synthetic musks, and thus less used so far. As personal care products are one of the main sources for the release of synthetic musks into the environment, it is noteworthy that the detection rates of musks in water correlate well with our previous study on the presence of synthetic musks in personal care products. In fact, HHCB, DPMI and EXA were the most detected[4].

While information about musks of the different classes is readily available in water, this is not true for the other matrices. For soil, only two publications that comply with our selection criteria were found (**Table S2**). No studies regarding the presence of the nitromusks MM, MT and MX and alicyclic or macrocyclic musks in Europe since 2000 were found, and therefore these compounds were not included in the risk assessment. The polycyclic musks, AHMI and HHCB were identified in all samples as well as the nitromusk MK, while ADBI, ATII, DPMI and MA were not detected. The highest levels were found for AHTN (up to 610 ng g^{-1}) and HHCB (up to 100 ng g^{-1}).

In outdoor air, three articles with data of 31 samples were retrieved (**Table S3**). Of all polycyclic musks, AHTN (100%), HHCB (100%) and ADBI (60%) where the predominantly detected. MA, MM and MT as well as the alicyclic or macrocyclic musks never reported and therefore excluded from further risk analysis. In line with the previous matrices, the highest levels were detected for HHCB (5900 – 10500 ng m^{-3}) and AHTN (1100 – 2400 ng m^{-3}) and surprisingly for MX (1600 – 4000 ng m^{-3}), although the latter result was obtained only for two samples[34].

For sediments (including suspended particle matter), three articles with a total of 48 samples were compiled in **Table S4**. In these studies only polycyclic musks were analysed. Therefore, no risk assessment for nitromusks and alicyclic or polycyclic musks in the sediments could be performed. The only musks found were HHCB (77%) AHTN (75%) and AHMI (9%), with AHTN occurring at highest levels (up to 1399 ng g^{-1}) followed by HHCB (maximum of 502 ng g^{-1}).

The dataset collected shows that there is still a need for more comprehensive studies about the occurrence of synthetic musks fragrances in Europe. Except for water, data regarding the newer generation alicyclic and polycyclic musks is still nonexistent and there is no insight about their incidence and mobility between environmental compartments. Due to the fact that nitromusks were banned or restricted in Europe, the focus on these chemicals has diminished, contributing to a lack of information about their legacy levels.

Environmental Risk

The environmental risk was evaluated combining the final score (which expresses the potential of a compound to have an impact on the environment) with its occurrence, given by the frequency of detection. A high risk occurs only when both parameters present high values simultaneously and the environmental risk is progressively attenuated as one or both conditions are less severe.

As can be seen at a first glance in **Fig. 3**, the positioning of the musks in the lower left half of the chart shows that the majority of the synthetic ones pose low or very low risk to the water compartment. In fact, none entails a very high risk. However, HHCB possesses a high risk (19.6), due to its high final score (23) and its relatively high occurrence (85.6%). Two other polycyclic musks that offer a medium risk are AHTN (11.6) and DPMI (6.8), although AHTN has a slightly higher risk as it occurs more often (83%) and has a higher impact potential (14.0). Of the nitromusks, only MX and MK present a low risk, while the others have very low risk, as they simply have not been detected in water samples. EXA (2.3) has a low risk as opposed to the other macrocyclic or alicyclic musks, due to its moderate score and low detection frequency, while the others were absent or hardly present in the matrix.

For soil, the lack of occurrence data prevented the evaluation of the environmental risk for nitromusks MX, MT, MM and all macrocyclic and alicyclic musks. According to **Fig. 4**, none of the studied musks offered a very high risk, but three pose a high risk: HHCB (24.0), AHMI (24.0) and MK (25.0). In all cases the combination of the high occurrence and a high score is responsible for this behaviour. AHTN has a similar final score (24.0), but since it only occurs in half of the samples, its risk is medium. As mentioned before, the number of studies in soil is scarce and the dataset is not as solid as in water. The case of AHTN is paradigmatic, as only a slight increase of its detection frequency (by 10%), which can easily happen as it is one of the most used musks[32] and more information is becoming available, can cause a significant change in the risk evaluation of this compound, from medium to high. All other musks showed very low risk, essentially due to their absence in the compartment, although their score was moderate (DPMI, MA) to high (ADBI, ATII).

Also for air the risk calculation suffered from the scarcity of the data available. Occurrence for macrocyclic and alicyclic musks could not be found, excluding these compounds from further evaluation. The same happened for MX, MT and MM. Still, the environmental risk of the ranked musks is quite varied (**Fig. 5**), ranging from very low for MM and ATII (due to absence in air) to very high for AHTN (16.0). The latter compound was found in all samples and has a high environmental impact potential, with a very high risk to environment. AHMI and ADBI have even higher hazardous potential, but as they only occur moderately, their environmental risk is medium.

Finally, for sediments, the risk assessment could only be performed for the polycyclic musks, but nevertheless provided a useful insight. As can be seen in **Fig. 6**, the valued musks showed high to very high potential risk scores. In this situation it is clear that the frequency of detention will definitely decide about the risks they pose to environment. DPMI, ADBI, ATII and AHMI showed low to very low risk, as their occurrence rates are between 0 and 16%. On the other side are HHCB (33.1) and AHTN (32.3), which pose a very high environmental risk to sediments. Both compounds showed the highest potential risk score (43) and had an occurrence frequency of about 80%.

CONCLUSIONS

The prioritisation approach presented in this study for synthetic musks shows that the same compound can pose quite diverse risks to different environmental compartments, as their potential risk score and frequency of detection can vary significantly. Nevertheless, some common findings can be drawn. In the four matrices considered, HHCB posed a high to very high risk, with the maximum in sediments (very high, 33.1), followed by soil (24.0) and water (19.6). In air the risk was high, achieving a score of 15.0 on its specific scale. AHMI has a risk to soil (24.0) and air (10.6), while the risk for sediments was low (3.8) and very low for water (0.0). While AHTN was considered to be of medium risk in the water and soil compartments, with final scores of 11.6 and 12.0, respectively, the same compound is prone to a very high risk in sediments (32.3) and air (16.0).

As mentioned previously, a risk evaluation without a dataset from a dedicated monitoring program is highly dependent on the quantity and quality of available information on the occurrence of the target compounds in the different environmental media. This is especially true for the macro and alicyclic musks, which are rather novel and therefore, still barely studied. Information on nitromusks is also lacking. However, this class of musks was partially banned or restricted in Europe. Therefore, most of the authors chose to leave them out of their studies. Borderline compounds, that is, those in which a small increase of detection frequency can cause a significant change of its risk, should be especially taken into account. Cases with scarce data availability are therefore more prone to uncertainties and variations as the information reported in literature becomes more abundant and solid.

Therefore, this kind of prioritisation can serve a double purpose. In a retrospective view, the combination of physicochemical and toxicological properties and occurrence data enables the estimation of the environmental impact posed by these compounds on different environmental compartments. This can be considered a basic environmental risk assessment, but still fit-for-purpose in many cases. In a prospective view, this approach can help to find borderline compounds, for which it is vital to clarify the level of risk they effectively pose. With these chemicals identified, monitoring efforts can be specifically designed to obtain information needed, avoiding non-targeted and consequently more expensive set-ups.

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Supporting Information

Supporting information may be found in the online version of this article.

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Table 1. Overall ranking of synthetic musks in the prioritization scheme for water.

	Compound	Bioaccumulation		Environmental Persistence							Ecotoxicity							Total Score	Impact
				Chemical Persistence		Mobility water-soil/sediment		Mobility water-air		Score	Fish		Daphnia		Algae		Score		
		BCF $_{fish}$ (L kg^{-1})	Score	$t_{1/2}$ (days)	Score	log K_{OC}	Score	H_C (atm m^{-3} mol^{-1})	Score		ChV (mg L^{-1})	Score	ChV (mg L^{-1})	Score	ChV (mg L^{-1})	Score			
1	Galaxolide (HHCB)	3631	**4**	60	4	4.29	2	$7.6x10^{-7}$	4	**3**	0.005	5	0.008	5	0.063	4	**5**	**23.0**	High
2	Musk muscone (MC)	3999	**4**	38	3	3.79	2	$4.9x10^{-4}$	3	**3**	0.008	5	0.012	4	0.088	4	**5**	**23.0**	High
3	Musk moskene (MM)	1675	**3**	180	5	4.31	2	$1.5x10^{-7}$	4	**4**	0.029	4	0.037	4	0.229	3	**4**	**22.0**	Moderate
4	Helvetolide (HELV)	2009	**4**	38	3	3.20	3	$4.5x10^{-6}$	4	**3**	0.024	4	0.031	4	0.198	3	**4**	**22.0**	Moderate
5	Exaltolide (EXA)	5333	**5**	15	2	3.68	2	$8.1x10^{-4}$	3	**2**	0.037[a]	4	0.031[b]	4	0.111[c]	3	**4**	**19.0**	Moderate
6	Traseolide (ATII)	1758	**3**	60	4	3.99	2	$1.9x10^{-5}$	3	**3**	0.004	5	0.007	5	0.059	4	**5**	**19.0**	Moderate
7	Musk tibetene (MT)	1216	**3**	60	4	4.05	2	$1.0x10^{-4}$	3	**3**	0.042	4	0.051	4	0.293	3	**4**	**18.0**	Moderate
8	Musk xylene (MX)	401	**2**	180	5	4.53	1	$7.7x10^{-9}$	5	**4**	0.196	3	0.201	3	0.901	3	**3**	**15.0**	Moderate
9	Musk ambrette (MA)	261	**2**	60	4	3.43	3	$7.1x10^{-7}$	4	**4**	0.309	3	0.295	3	1.207	2	**3**	**15.0**	Moderate
10	Celestolide (ADBI)	984	**2**	60	4	3.71	2	$7.1x10^{-6}$	4	**3**	0.009	5	0.013	4	0.095	4	**5**	**14.0**	Moderate
11	Phantolide (AHMI)	986	**2**	60	4	3.69	2	$7.7x10^{-6}$	4	**3**	0.010	5	0.015	4	0.106	3	**5**	**14.0**	Moderate
12	Tonalide (AHTN)	697	**2**	60	4	3.94	2	$1.4x10^{-4}$	3	**3**	0.004	5	0.007	5	0.056	4	**5**	**14.0**	Moderate
13	Ethylene Brassylate (EB)	597	**2**	15	2	2.85	3	$1.5x10^{-7}$	4	**3**	0.107	3	0.116	3	0.570	3	**3**	**12.0**	Low
14	Romandolide (ROM)	404	**2**	38	3	2.61	3	$6.7x10^{-6}$	4	**3**	0.177	3	0.181	3	0.815	3	**3**	**12.0**	Low
15	Cashmeran (DPMI)	427	**2**	38	3	3.01	3	$1.4x10^{-4}$	3	**3**	0.126	3	0.130	3	0.592	3	**3**	**12.0**	Low
16	Ambrettolide (AMB)	1629	**3**	15	2	3.94	2	$3.0x10^{-4}$	3	**2**	0.194[a]	3	0.150[b]	3	0.406[c]	3	**3**	**12.0**	Low
17	Musk ketone (MK)	83	**1**	60	4	3.40	3	$1.9x10^{-9}$	5	**4**	0.254	3	0.251	3	1.080	2	**3**	**9.0**	Low
18	Globalide (GLO)	773	**2**	15	2	3.68	2	$1.9x10^{-4}$	3	**2**	0.506[a]	3	0.375[b]	3	0.839[c]	3	**3**	**9.0**	Low

[a] Acute toxicity - $LC_{50\ fish}$; [b] Acute toxicity - $LC_{50\ daphnia}$; [c] Acute toxicity - $EC_{50\ algae}$

Table 2. Overall ranking of synthetic musks in the prioritization scheme for soil.

	Compound	**Bioaccumulation**		**Environmental Persistence**							**Ecotoxicity**		**Total Score**	**Impact**
				Chemical Persistence		**Mobility soil-water**		**Mobility soil-air**		**Score**	**Earthworm**			
		BCF $_{earthworm}$ (L kg^{-1})	**Score**	**$t_{1/2}$ (days)**	**Score**	**log K_{OC}**	**Score**	**log K_{SA}**	**Score**		**ChV (mg L^{-1})**	**Score**		
1	Musk xylene (MX)	339	**4**	360	5	4.5	4	9.1	5	**5**	288	**1**	**31.0**	High
2	Musk moskene (MM)	2946	**5**	360	5	4.3	4	7.6	4	**4**	215	**1**	**31.0**	High
3	Musk ketone (MK)	240	**4**	120	3	3.4	3	8.6	5	**4**	295	**1**	**25.0**	High
4	Celestolide (ADBI)	10214	**5**	120	3	3.7	4	5.3	2	**3**	166	**1**	**24.0**	High
5	Phantolide (AHMI)	8496	**5**	120	3	3.7	4	5.3	2	**3**	169	**1**	**24.0**	High
6	Traseolide (ATII)	24502	**5**	120	3	4.0	4	5.2	2	**3**	161	**1**	**24.0**	High
7	Galaxolide (HHCB)	9533	**5**	120	3	4.3	4	6.9	3	**3**	177	**1**	**24.0**	High
8	Tonalide (AHTN)	6015	**5**	120	3	3.9	4	4.2	1	**3**	186	**1**	**24.0**	High
9	Musk tibetene (MT)	1817	**5**	120	3	4.1	4	4.5	1	**3**	217	**1**	**24.0**	High
10	Musk muscone (MC)	10945	**5**	75	3	3.8	4	3.6	1	**3**	161	**1**	**24.0**	High
11	Musk ambrette (MA)	178	**4**	120	3	3.4	3	6.0	2	**3**	278	**1**	**19.0**	Moderate
12	Ethylene Brassylate (EB)	616	**4**	30	2	2.8	3	6.1	3	**3**	246	**1**	**19.0**	Moderate
13	Exaltolide (EXA)	16951	**5**	30	2	3.7	4	3.2	1	**2**	155[a]	**1**	**16.0**	Moderate
14	Ambrettolide (AMB)	2814	**5**	30	2	3.9	4	3.9	1	**2**	196[a]	**1**	**16.0**	Moderate
15	Helvetolide (HELV)	3884	**5**	75	3	3.2	3	5.0	1	**2**	214[a]	**1**	**16.0**	Moderate
16	Cashmeran (DPMI)	372	**4**	75	3	3.0	3	3.3	1	**2**	198[a]	**1**	**13.0**	Moderate
17	Romandolide (ROM)	339	**4**	75	3	2.6	3	4.3	1	**2**	262[a]	**1**	**13.0**	Moderate
18	Globalide (GLO)	911	**4**	30	2	3.7	4	3.9	1	**2**	208[a]	**1**	**13.0**	Moderate

[a] Acute toxicity measured by LC_{50}

Table 3. Overall ranking of synthetic musks in the prioritization scheme for air.

	Compound	Bioaccumulation		Environmental Persistence								
				Chemical Persistence		Mobility air-soil		Mobility air-water		Deposition potential		Sco
		BCF $_{plant}$ (unitless)	Score	$t_{1/2}$ (days)	Score	log K_{SA}	Score	H_C (atm m^{-3} mol^{-1})	Score	Ø (%)	Score	
1	Celestolide (ADBI)	$3.27x10^7$	**5**	1.438	3	5.3	4	$7.05x10^{-6}$	2	0.26	5	**4**
2	Phantolide (AHMI)	$2.72x10^7$	**5**	0.704	3	5.3	4	$7.73x10^{-6}$	2	0.24	5	**4**
3	Traseolide (ATII)	$5.92x10^7$	**5**	0.550	3	5.2	4	$1.94x10^{-5}$	3	0.45	5	**4**
4	Musk ambrette (MA)	$1.28x10^9$	**5**	7.125	4	6.0	4	$7.05x10^{-7}$	2	3.52	5	**4**
5	Musk tibetene (MT)	$6.37x10^8$	**5**	7.292	4	4.5	5	$9.96x10^{-5}$	3	3.44	5	**4**
6	Helvetolide (HELV)	$1.10x10^7$	**5**	0.345	2	5.0	5	$4.45x10^{-6}$	2	0.17	5	**4**
7	Tonalide (AHTN)	$4.41x10^6$	**4**	0.604	3	4.2	5	$1.39x10^{-4}$	3	0.51	5	**4**
8	Exaltolide (EXA)	$7.45x10^5$	**4**	0.558	3	3.2	5	$8.10x10^{-4}$	3	2.93	5	**4**
9	Romandolide (ROM)	$1.55x10^6$	**4**	0.738	3	4.3	5	$6.74x10^{-6}$	2	0.07	5	**4**
10	Musk muscone (MC)	$1.28x10^6$	**4**	0.359	2	3.6	5	$4.88x10^{-4}$	3	0.22	5	**4**
11	Ethylene Brassylate (EB)	$2.02x10^7$	**5**	0.625	3	6.1	3	$1.51x10^{-7}$	2	60.20	3	**3**
12	Galaxolide (HHCB)	$7.38x10^6$	**5**	0.283	2	6.9	3	$7.56x10^{-7}$	2	0.33	5	**3**
13	Musk ketone (MK)	$5.08x10^{10}$	**5**	8.292	4	8.6	1	$1.90x10^{-9}$	1	19.30	4	**3**
14	Musk xylene (MX)	$3.31x10^{10}$	**5**	12.875	4	9.1	1	$7.73x10^{-9}$	1	29.30	4	**3**
15	Musk moskene (MM)	$1.47x10^9$	**5**	6.083	4	7.6	2	$1.54x10^{-7}$	2	5.70	5	**3**
16	Ambrettolide (AMB)	$1.06x10^5$	**3**	0.041	1	3.9	5	$3.01x10^{-4}$	3	6.19	5	**4**
17	Globalide (GLO)	$8.52x10^4$	**3**	0.274	2	3.9	5	$1.90x10^{-4}$	3	3.17	5	**4**
18	Cashmeran (DPMI)	$2.66x10^5$	**3**	0.090	2	3.3	5	$1.42x10^{-4}$	3	0.02	5	**4**

Table 4. Overall ranking of synthetic musks in the prioritization scheme for sediments.

	Compound	Bioaccumulation		Environmental Persistence					Ecotoxicity		Total Score
				Chemical Persistence		Mobility sediment-water		Score	Daphnia		
		BCF $_{benthic}$ (unitless)	Score	$t_{1/2}$ (days)	Score	log K_{OC}	Score		ChV (mg L^{-1})	Score	
4	Traseolide (ATII)	10517	**5**	542	5	3.99	4	**5**	0.007	**5**	**43.0**
5	Galaxolide (HHCB)	4854	**5**	542	5	4.29	4	**5**	0.008	**5**	**43.0**
6	Tonalide (AHTN)	3329	**5**	542	5	3.94	4	**5**	0.007	**5**	**43.0**
2	Celestolide (ADBI)	5137	**5**	542	5	3.71	4	**5**	0.013	**4**	**42.0**
3	Phantolide (AHMI)	4417	**5**	542	5	3.69	4	**5**	0.015	**4**	**42.0**
10	Musk tibetene (MT)	1249	**5**	542	5	4.05	4	**5**	0.051	**4**	**42.0**
11	Musk moskene (MM)	1855	**5**	1621	5	4.31	4	**5**	0.037	**4**	**42.0**
15	Musk muscone (MC)	5436	**5**	338	5	3.79	4	**5**	0.012	**4**	**42.0**
12	Exaltolide (EXA)	7778	**5**	135	4	3.68	4	**4**	0.031	**4**	**34.0**
18	Helvetolide (HELV)	2326	**5**	338	5	3.20	3	**4**	0.031	**4**	**34.0**
7	Musk xylene	315	**4**	1621	5	4.53	5	**5**	0.201	**3**	**33.0**

	(MX)										
16	Ambrettolide (AMB)	1787	**5**	135	4	3.94	4	**4**	0.150	**3**	**33.0**
1	Cashmeran (DPMI)	340	**4**	338	5	3.01	3	**4**	0.130	**3**	**27.0**
8	Musk ambrette (MA)	186	**4**	542	5	3.43	3	**4**	0.295	**3**	**27.0**
9	Musk ketone (MK)	238	**4**	542	5	3.40	3	**4**	0.251	**3**	**27.0**
13	Ethylene Brassylate (EB)	515	**4**	135	4	2.85	3	**4**	0.116	**3**	**27.0**
14	Romandolide (ROM)	315	**4**	338	5	2.61	3	**4**	0.181	**3**	**27.0**
17	Globalide (GLO)	709	**4**	135	4	3.68	4	**4**	0.375	**3**	**27.0**