Food and Chemical Toxicology 104 (2017) 57–68

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

# Occurrence and toxicity of musks and UV filters in the marine environment

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ARTICLE INFO

*Article history:*
Received 5 September 2016
Received in revised form
10 November 2016
Accepted 12 November 2016
Available online 12 November 2016

*Keywords:*
Musks
UV filters
Toxicity
Marine

ABSTRACT

Emerging chemical contaminants in the marine ecosystem represent a threat to the environment and also to human health due to insufficient knowledge about their toxicity and bioaccumulation in the food chain. Consequently, many of them are not regulated. In this review we focus on musks and organic UV filters. For both groups of compounds we describe occurrence in the marine environment, toxic effects identified so far and methods used to identify such effects. The final objective of this work is to identify gaps in the understanding of their toxicology.



## 1. Introduction

The production of man-made synthetic chemical compounds has largely increased after the Second World War. These compounds have been synthesized to answer needs for substances having specific properties demanded principally by the industry and agriculture. The dark side of chemical expansion begins with problems related to compounds' fate upon release into the environment and waste disposal. Since these compounds are evolutionary new, biota and especially microorganisms have not yet adapted their metabolic pathways to efficiently degrade and remove them from the environment, as suggested for bacterial dehalogenases (Janssen et al., 2005). Therefore, they tend to further accumulate, posing risk to the environment and biota health status. Resistance to degradation is even more pronounced for lipophilic substances. Additionally, these substances have a natural tendency to accumulate in non-polar lipid tissues, consequently becoming persistant environmental contaminants. Their biomagnification through the food chain finally affects organisms on the higher trophic levels, including humans.

The term emerging contaminant has been adopted for those substances that have not been historically considered as contaminants. However, many are produced industrially and are commonly derived from municipal, agricultural, and industrial wastewater sources and pathways. Their toxicity can be studied by a battery of *in vitro* methods based on cells cultivated in special culture media, as well as by a variety of invertebrate and vertebrate animal models *in vivo*. Cell lines upon exposure to substances under study provide basic data on molecular toxicity mechanisms, measured by changes in the gene expression, altered physiology and metabolism, cell death or other organ specific endpoints (Bouvier d'Yvoire et al., 2012; Wallace, 2012). However, cell lines derived from different tissues should be used to eliminate potential false negatives as a consequence of tissue specific adverse effects. Cell cultures *in vitro* represent an overall simplified model of the real situation, where complex endocrine hormonal pathways and active communication between distant organs direct coordination at the organism level. Organ specific differentiated cells may lack specific receptors, transporters and metabolic pathways present in other tissues, therefore experiments using different cell lines are more reliable. To obtain better insights into the mode of action, transgenic cell lines are also used. Biological systems used in ecotoxicology are generally related to the type of effect that one wants to measure and animal model selection generally depends on the type of environment to test. Aquatic toxicology is one of the major branches in ecotoxicology since earth's surface is being water-covered by three fourths. Animal models relevant in aquatic toxicology are mainly fish belonging to different species; however, a

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http://dx.doi.org/10.1016/j.fct.2016.11.012
0278-6915/

variety of invertebrates such as daphnids, crustaceans such as copepods (Raisuddin et al., 2007) and mussels are also used. Rainbow trout (*Oncorhynchus mykiss*) and fathead minnows (*Pimephales promelas*) are among the most extensively studied freshwater species in aquatic toxicology (Abbott, 2013). Some animal models are versatile and allow testing of endpoints relevant to both environmental and human health. This is the case of zebrafish (*Danio rerio*), that is an acknowledged model in ecotoxicology, but also widely used as a model of various human diseases (cancer, neurotoxicity, etc.) with application in a variety of fields such as pharmacology, physiology, neurology and developmental biology (see for example Phillips and Westerfield (2014); Sogorb et al. (2014)). Medaka (*Oryzias latipes*) is also considered a versatile model being a vertebrate that can be used for both human and environmental toxicity assessment (Naruse et al., 2011). However, one of the limitations of these species is that they are freshwater fish and therefore they are not always predictive of the effects found in marine organisms. Saltwater fish are generally less studied than freshwater fish due to the fact that it is harder to maintain them in laboratory conditions. As an exception, Atlantic salmon (*Salmo salar*) is a marine fish that has been intensively studied (Abbott, 2013). For the study of marine environments a very promising model seems to be marine medaka (*Oryzias melastigma*). As a matter of fact, this species presents the same advantages as freshwater medaka. The two species are genetically very close, therefore the genetic tools and knowledge available for the freshwater species can be conveniently used for the marine counterpart (Dong et al., 2014).

It is important to note that animal models can not be considered absolutely reliable to predict human toxicity. More, due to ethical reasons regulatory organs worldwide encourage development and use of *in vitro* toxicity models, complying with the 3R (reduce, refine, replace) principle originally developed more than 50 years ago (Russell and Burch, 1959). Concentrations of substances that cause measurable changes in the endpoint assays both *in vitro* and *in vivo* are usually provided as EC (Effective Concentration), IC (Inhibitory Concentration), PNEC (Predicted No Effect Concentration) and LOEC (Lowest Observed Effective Concentration). EC and IC are more applicable to describe endpoints measured by *in vitro* models, while EC, PNEC and LOEC are widely used to describe effects obtained by animal models *in vivo*.

In the present review, we are focusing on two emerging groups of contaminants, known as musks and UV filters (UVFs) according to their properties and intended use. Musks and UVFs are mainly added to a wide variety of industrial and household articles, but UVFs can also be found in paints. In general, they are substances with lipophilic properties having a potential for bioaccumulation. We present data on their marine occurrence, concentrations as well as toxicity data obtained by *in vitro* experiments and animal tests. Moreover, we discuss problems related to their toxicological assessment and try to identify current knowledge gaps that need to be answered by future research.

## 2. Musks

One of the most widespread personal care products (PCP) are synthetic musks, incorporated in many household commodities, ranging from perfumes, shampoos, lotions, washing powders and deodorants (Nakata et al., 2015). Invariably they are not listed as ingredients of these products but rather included under the terms perfume or fragrance. Synthetic musks have been created as a replacement for rare and expensive natural musks obtained from musk deer and musk ox. Based on their chemical structure they are classified as nitro, polycyclic, macrocyclic and alicyclic musks (Kraft, 2004) (Fig. 1). Nitro musks have already been largely removed from the market due to environmental and toxicological concerns and have been replaced by compounds belonging to the other three groups. Currently, polycyclic musks are dominating, followed by macrocyclic musks occupying a small fraction of the market, while the use of alicyclic musks is almost negligible (Homem et al., 2015).

Musks can potentially enter the human body through skin penetration, inhalation and food ingestion. Mostly they are discarded into waste water, but waste water treatment plants can not completely remove some of the polycyclic musks, namely galaxolide, tonalide and macrocylic musk ambrettolide (Vallecillos et al., 2014). Therefore, they are frequently found in surface water, lakes and estuaries (Lange et al., 2015; Liu and Wong, 2013; Melymuk et al., 2014). In addition to galaxolide and tonalide, celestolide (ADBI), phantolide (AHMI), musk xylene (MX) and musk ketone (MK) have been reported in estuarine and coastal waters from all around the world (Casatta et al., 2015; Combi et al., 2016; Dsikowitzky et al., 2016; Sumner et al., 2010). Through wastewater, musks reach the marine environment and due to their lipophilic nature they tend to bioccumulate in aquatic biota (Hu et al., 2011; Lee et al., 2014). However, it is expected that higher concentrations of musks in biota are found in rivers and coastal regions in highly populated urban areas close to sewage treatment plants, as confirmed by Lee et al. (2014).

### 2.1. Nitro musks

The synthetic nitro musks known as musk ambrette and musk tibetene have already been banned from use in the EU cosmetics industry, while MK and MX are allowed in defined concentrations in personal care products with the exception of oral care products (European Parliament, 2009a). Moreover, in the frame of EU valid REACH chemical regulation (European Parliament, 2009b), MX is considered as very persistent and very bioaccumulative (vPvB). Since MK and MX are the only nitro musks found in the marine environment (see section 2), we further consider them as relevant for toxicity evaluation. Since nitro musks were first in use, several authors in the period between 1990 and 2000 reported significant amounts of these compounds in marine fish (Gatermann et al., 1999; Rimkus et al., 1999, 1997; Rimkus and Wolf, 1995), but lately, most of the studies have not detected MK and MX in marine fish samples (Foltz et al., 2014) and higher animals (Guerranti et al., 2014). In contrast to polycyclic musks, nitro musks have been found at very low or even below quantification limits in marine mammals and sharks from Japanese coastal waters (Nakata, 2005). Despite fears of biomagnification, comparison of biota-sediment accumulation factor of musks including MK and MX suggested that musks in bivalves are not biomagnified via the food chain, but mostly partitioned from sediment (Lee et al., 2014). Nitro musks are lipophilic substances, therefore they have been found in human fat and breast milk samples, but maternal age does not correlate with concentrations in milk (Rimkus et al., 1994), as expected for bioaccumulating substances. Later studies have frequently showed presence of MX and MK in human milk and blood (Den Hond et al., 2013; Kang et al., 2010; Schlumpf et al., 2010; Zhang et al., 2015). Blood plasma levels of MX were found up to 190 ng/L in Austrian women, with higher concentrations found in women after the age of 50 (Hutter et al., 2010). Presumably, these levels are more related to the use of cosmetics than food itself. Upon absorption in the body, nitro musks undergo metabolisation. MX in humans is converted into 4-amino MXT that binds to haemoglobin and is also secreted in urine with an average half-life of 70 days (Riedel and Dekant, 1999). 4-amino MX, 2-amino MX and 2-amino MK as metabolic products have been demonstrated in water samples and biota (Rimkus et al., 1999). MX administration to developing rats